In the United States Court of Federal Claims

No. 15-792
(Filed: 31 October 2022[*])

HEATHE HELLER and JENNA HELLER, as parents of H.H., a Minor,	*	
Petitioners,	*	Vaccine Act; Off-Table; Aicardi-Goutières Syndrome; AGS; Type I Interferonopathy; Significant Aggravation; Genetic Mutation; *Loving*; Pentacel.
v.	*	
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

Margaret M. Guerra, Attorney at Law, Fort Worth, TX, for petitioners.

Tyler King, Vaccine/Torts Branch, Civil Division, U.S. Department of Justice, Washington, DC, for respondent.

OPINION AND ORDER

HOLTE, Judge.

This case involves the injury of a child with a suspected pre-existing genetic mutation. Congress designed the Vaccine Act as part of "the Nation's efforts to protect its children by preventing disease." *Cloer v. Sec'y of Health & Hum. Servs.*, 654 F.3d 1322, 1325 (Fed. Cir. 2011) (quoting H.R. Rep. No. 99-908, at 4 (1986)). "[W]hile most of the Nation's children enjoy a greater benefit from immunization programs, a small but significant number have been gravely injured." *Id.* Congress created the Vaccine Program to "compensate injured persons quickly and fairly" for injuries "either presumed or proven to be causally connected to vaccines." *Id.*

Petitioners Heathe Heller and Jenna Heller ("petitioners"), on behalf of their son, H.H., filed a petition for compensation under the National Vaccine Injury Compensation Program, 42 U.S.C. § 300aa-10, *et seq.* *See* Pet., ECF No. 1. Petitioners allege H.H.'s 15-month vaccinations caused or significantly aggravated H.H.'s degenerative neurological disorder. *Id.* The Special Master, in her Decision for Entitlement, denied petitioners' request because petitioners were

[*] This opinion was initially filed under seal on 13 October 2022 pursuant to Vaccine Rule 18(b) of the Rules of the Court of Federal Claims. The Court provided the parties 14 days to submit proposed redactions, if any, before the opinion was released for publication. Neither party proposed redactions. This opinion is now reissued for publication in its original form.

unable to preponderantly establish the vaccinations caused or significantly aggravated H.H.'s injury. SM Dec. 74, ECF No. 121. Petitioners filed a motion for review with an accompanying memorandum asking the Court for review of the Special Master's decision denying the petition. *See* Mot. for Review, ECF No. 122; Mot. for Review Mem., ECF No. 123. According to petitioners, the Special Master erroneously diagnosed H.H. with a genetically caused Aicardi–Goutières Syndrome ("AGS") or AGS-like type I interferonopathy, altering the *Loving/Althen* causation in fact analyses against the significant evidence proffered by petitioners. Mot. for Review Mem. at 1. For the following reasons, the Court **GRANTS** petitioners' motion in part, **VACATES** the Special Master's decision in part, and **REMANDS** this case to the Special Master for further proceedings consistent with this opinion.

I. Petitioners' Medical History and the Vaccination

As the basic facts have not changed significantly from petitioners' original claim to their appeal, the Court's recitation of the background facts draws from the Special Master's Decision of Entitlement ("SM Dec.").[1] H.H. was born on 14 July 2012. Pet'rs' Ex. 48.1, ECF No. 40-1 (Birth Certificate). Except for an abnormal newborn screen indicating a very long-chain acyl-CoA dehydrogenase ("VLCAD") deficiency, a condition in which the body is unable to properly break down certain fats into energy, H.H.'s well-child visits were normal, and H.H. was meeting developmental milestones. Pet'rs' Ex. 49.2 at 7–34, ECF No. 40-2 (Dr. Hollis Notes, pages 1–42). On 29 July 2013, when H.H. was a year old, Dr. Hollis, a pediatrician, saw H.H. for a sick-child visit due to a fever and nasal congestion. *Id.* at 36. On 13 September 2013, Ms. Heller called H.H.'s pediatrician's office because H.H. was not walking, and his right foot turned inward. *Id.* at 37. The office suggested the problem be discussed further at H.H.'s upcoming 15-month appointment. *Id.*

At his 15-month well visit, Dr. Hollis noted H.H. was meeting all development milestones, and there were no physical abnormalities. *Id.* at 1–2. H.H. also received the influenza and pneumonia vaccines at the 15-month appointment. *Id.* He was supposed to receive the DTaP-IVH-Hib (Pentacel) vaccine as well, but the office was out of Pentacel, so H.H. returned on 23 October 2013 to receive the vaccine. *Id.* at 3. On 11 November 2013, H.H. was fussy, running a fever, and had decreased energy levels. Pet'rs' Ex. 49.2 at 41. Dr. Hollis noted H.H. had regressed in the last month, explaining he stopped crawling, lost interest in playing with toys, and threw food. *Id.* At the conclusion of the appointment, H.H. was diagnosed with developmental delay and acute pharyngitis and was referred to neurology for evaluation. *Id.* The next day, H.H. visited Dr. Crawford, a geneticist, who noted elevated transaminase levels and developmental delays. Pet'rs' Ex. 50.4 at 1–2, ECF No. 40-4 (Dr. Crawford Notes, pages 1–27). Dr. Crawford ordered genetic and metabolic workups as well as a magnetic resonance imaging ("MRI") and recommended physical and speech therapy. *Id.* at 2. On 14 November 2013, H.H. was admitted to the hospital where physicians found "significant dystonic posturing of the lower extremities." Pet'rs' Ex. 51.6 at 5, ECF No. 40-6 (Cook's Radiology Records). H.H. was treated and discharged on 16 November 2013. *Id.*

[1] In describing the background of petitioners' claim, the Court refers primarily to the special master's factual background as recited in the decision for entitlement. *See* SM Dec. at 5–27. Petitioners do not assert error in the facts as stated by the Special Master, but rather challenge the legal conclusions drawn from those facts. *See generally* Mot. for Review.

On 22 November 2013, Dr. Aalbers, a neurologist, saw H.H. and noted H.H. had lost meaningful use of his right hand since his discharge on 16 November 2013. Pet'rs' Ex. 52.7 at 9, ECF No. 40-7 (Dr. Aalbers Notes, pages 1–34). Dr. Aalbers believed H.H. had "rapidly progressive ascending dystonia with encephalopathy" and was concerned with mitochondrial disease. *Id.* at 11. On 23 November 2013, H.H. underwent genetic testing, and the results did not show any "deletions or duplications of known or potential clinical significance." Pet'rs' Ex. 50.5 at 61, ECF No. 40-5 (Dr. Crawford Notes, pages 26–66). On a 3 December 2013 visit, Dr. Aalbers definitively diagnosed H.H. with "rapidly progressive dystonia and encephalopathy" with "concern for possible Aicardi-Goutières [syndrome ('AGS').]" Pet'rs' Ex. 52.7 at 28. To confirm a diagnosis, Dr. Aalbers arranged for human immunodeficiency virus ("HIV") testing, ordered a second round of neurotransmitter studies, and referred H.H. to Dr. Crawford for additional genetic testing. *Id.* On 3 December 2013, Dr. Crawford noted H.H.'s neopterin and tetrahydrobiopterin were significantly elevated, and the lab stated, "only Aicardi-Goutieres syndrome and HIV infection would cause such high values." Dr. Crawford Notes, pages 1–27 at 12. Dr. Crawford noted H.H. "does not have [a] typical presentation of AGS[;] . . . however, there are milder presentation[s] of this syndrome . . . . Therefore, this disorder remains on our differential." *Id.* She received permission from H.H.'s family to contact an AGS expert in England, Dr. Yanick Crow, and recommended intensive therapies. *Id.*

On 18 December 2013, H.H. visited Dr. Richard Roberts, a neurosurgeon, for a consultation regarding H.H.'s tethered spinal cord, revealed after an MRI showed "a thickened and fat infiltrated filum terminale." Pet'rs' Ex. 53.9 at 7, ECF No. 40-9 (Dr. Roberts Notes, pages 1–10). H.H. underwent surgery to release his tethered spinal cord the next day, and the cerebrospinal fluid taken during surgery showed "remarkably high elevations of biopterin and neopterin"—the highest levels Dr. Aalbers had ever seen. *Id.* at 7–8; Pet'rs' Ex. 55.2 at 1, ECF No. 41-2 (Drs. Aalbers and Cantu Notes, pages 1–20). Dr. Aalbers noted the differential diagnosis in a patient with high levels of neopterin, elevated liver enzymes, and dystonia was likely "Aicardi-Goutières syndrome," even though the genetic disorder was incredibly rare. *Id.* at 1, 4. Dr. Aalbers ordered additional testing in the hospital which showed an abnormal electroencephalogram "consistent with Aicardi-Goutieres syndrome." *Id.* at 3–4. While still in the hospital, Lori Thompson, a Certified Pediatric Nurse Practitioner ("CPNP"), saw H.H. regarding his elevated transaminases. Pet'rs' Ex. 54.1 at 1, ECF No. 41-1 (Dr. Thompson Notes, pages 1–6). Nurse Thompson noted AGS was a concern and H.H. would undergo neurological and gastroenterological testing to reevaluate his liver transaminases. *Id.* On 17 January 2014, Dr. Samson Cantu, a gastroenterologist, saw H.H. for abnormal liver enzymes, and the testing ordered revealed low globulin, a high albumin/globulin ratio, low bilirubin, high aspartate transaminase ("AST"), and high alanine transaminase ("ALT") levels. Pet'rs' Ex. 55.2 at 9; Pet'rs' Ex. 80.8 at 8, ECF No. 45-8 (Dr. Cantu Notes, pages 1–68).

On 4 February 2014, Dr. Marks, a pediatric neurologist, reviewed the results of the neurological and genetic testing and indicated AGS was the likely diagnosis but was awaiting genetic confirmation. Pet'rs' Ex. 56.3 at 4, ECF No. 41-3 (Dr. Marks Notes, pages 1–45). Dr. Crawford, the geneticist, saw H.H. the same day and noted H.H. "appears to have a later-onset presentation for AGS," but genetic testing was ongoing in England. Pet'rs' Ex. 50.4 at 23–24. On 6 March 2014, H.H. received the results of his genetic testing, which indicated one

significant mutation, a VLCAD deficiency in the gene acyl-CoA dehydrogenase very long chain ("ACADVL"). Pet'rs' Ex. 50.5 at 40. Dr. Marks noted H.H. could have "possible AGS" but with an unidentified genetic marker. Pet'rs' Ex. 56.3 at 18.

On 25 March 2014, after repeat testing, H.H.'s neopterin was extremely elevated, and Dr. Hyland, Director of Labcorp's Department of Neurochemistry Medical Neurogenetics Laboratories, interpreted the testing and noted the findings were consistent with a diagnosis of AGS. Pet'rs' Ex. 56.11 at 360–61, ECF No. 41-11 (Dr. Marks Notes, pages 342–387). On 23 April 2014, Dr. Cantu, the gastroenterologist, noted H.H. had an "extensive work-up by neurology with unclear diagnosis, although it has been suggested he may have a variant of Aicardi." Pet'rs' Ex. 61.8 at 13, ECF No. 42-8 (Dr. Marks Notes, pages 1–26). On 24 April 2014, Dr. Marks, the pediatric neurologist, diagnosed H.H. with "[p]rogressive encephalopathy and dystonia with loss of milestones and worsening dystonia[,] [and] [i]nterferonopathy with elevated neopterin clinically suggestive of Aicardi-Goutière[s] [s]yndrome but with negative genetic testing." Pet'rs' Ex. 56.10 at 328, ECF No. 41-10 (Dr. Marks Notes, pages 297–341). Dr. Marks recommended intravenous immune globulin ("IVIG") treatment, which H.H. began in June. *Id.* at 329. On 3 November 2014, H.H.'s testing showed elevated Immunoglobulin G ("IgG") serum, elevated indocyanine green ("ICG")/albumin ratio, high neopterin, and high tetrahydrobiopterin. *Id.* at 323–24. The nurse who completed the pre-procedure nursing record on behalf of Dr. Marks noted H.H. suffered from "autoimmune response to vaccines." Pet'rs' Ex. 56.6 at 106, ECF No. 41-6 (Dr. Marks Notes, pages 96–145).

On 20 March 2015, H.H. visited the Myelin Disorders Clinic at Children's National Hospital in Washington, DC and saw Dr. Adeline Vanderver, the director of the clinic, who planned to follow up with Dr. Crow, the clinical scientist in England specializing in AGS research, to discuss H.H.'s suspected heritable interferonopathy. Pet'rs' Ex. 81.9 at 6, ECF No. 45-9 (Dr. Vanderver Notes, pages 1–10). On 4 March 2016, H.H. saw Dr. Marc Mazade, an infectious disease specialist, who noted H.H. was "diagnosed with encephalitis of an autoimmune nature presumably due to vaccinations two weeks previously." Pet'rs' Ex. 95 at 54, 56–57, ECF No. 61 (Medical Records). On 15 November 2016, H.H. saw Dr. Abigail Collins, a pediatric neurologist, for treatment with medical marijuana. Pet'rs' Ex. 98, ECF No. 93-2 (Medical Records). On 8 December 2016, H.H. underwent hip surgery to alleviate hip tightness associated with his neuromuscular hip dysplasia. Pet'rs' Ex. 95 at 199.

On 26 June 2017, Dr. Marks found H.H. had elevated glucose levels, but his neopterin and tetrahydrobiopterin levels were normal. Pet'rs' Ex. 95 at 77. An MRI showed H.H. had lost white matter over the past three years. *Id.* at 147. On 9 July 2017, H.H. visited the emergency room with complaints of seizures. *Id.* at 105. Doctors were unable to determine the origin of the seizure. *Id.* at 135. H.H. was discharged on 11 July 2017, and the discharge summary noted Dr. Marks would seek approval for an experimental use drug for AGS. *Id*. at 130–31. On 23 August 2017, H.H. underwent stem cell treatment in Panama. *Id.* at 18. Upon return to the United States, during a 29 November 2017 visit, Dr. Marks noted H.H.'s hypertonia had improved and characterized H.H.'s disorder as "interferonopathy with elevated neopterin clinically consistent [with] Aicardi-Goutière[s] Syndrome or other autoimmune mediated event." Pet'rs' Ex. 96 at 6, ECF No. 77-1 (Cook Children's Medical Records, pages 1–115). During a 1 October 2018 visit, Dr. Marks described H.H.'s condition as "presumed Aicardi-Goutière[s] syndrome." *Id.* at 2.

On 10 December 2018, Dr. Marks noted H.H.'s dystonia worsened, and on 23 January 2019, H.H.'s condition remained unchanged from his 10 December 2018 appointment. *Id.* at 6, 11–12. H.H.'s MRI on 23 January 2019 showed "no significant change of already existing abnormalities" and "for Aicardi-Goutières syndrome, the severity of findings was quite mild." *Id.* at 16. Additionally, H.H.'s neopterin and tetrahydrobiopterin levels were elevated. *Id.* at 14. On 22 July 2019, H.H. was admitted to the hospital for seizure-like activity. *Id.* at 17. On 4 September 2019, Dr. Marks saw H.H. whose condition was largely unchanged from his 23 January 2019 appointment. *Id.* at 58–60.

II. The Petition and Procedural History Before the Special Master

Heathe and Jenna Heller, on behalf on their minor son, H.H. filed a petition on 27 July 2015 alleging H.H.'s influenza, pneumonia, and DTaP-IVH-Hib (Pentacel) vaccinations caused or significantly aggravated H.H.'s neurological disorder. *See* Pet. Petitioners filed all relevant medical records, affidavits, and expert reports from treating physicians Dr. Leslie Hollis and Dr. Warren Marks, *see* ECF Nos. 19, 14, and 16, and the record was complete on 9 November 2015. *See* Statement of Completion, ECF No. 17. The government filed its Rule 4(c) Report alleging the case was not appropriate for compensation and should be dismissed on 1 February 2016. *See* Resp't's Rule 4(c) Rep., ECF No. 21. Petitioners filed additional affidavits and a supplemental expert report from Dr. Hollis on 21 March 2016. Notice of Filing, ECF No. 28 (Updated Table of Contents and Exhibit List). After a status conference with Special Master Hasting, petitioners renumbered and refiled all previously submitted medical records, affidavits, and expert reports. Notice of Filing, ECF No. 40 (Exhibits 48–53); Notice of Filing, ECF No. 41 (Exhibits 54–56); Notice of Filing, ECF No. 42 (Exhibits 57–63); Notice of Filing, ECF No. 43 (Exhibits 64–69); Notice of Filing, ECF No. 44 (Exhibits 70–73); Notice of Filing, ECF No. 45 (Exhibits 74–83); Notice of Filing, ECF No. 46 (Exhibits 84–93). The government filed an expert report from Dr. Kristin Barañano with supporting medical literature on 14 December 2016. Barañano Expert Rep., ECF No. 52. Petitioners filed a supplemental expert report from Dr. Warren Marks on 25 August 2017. Marks Expert Rep., ECF No. 54.

On 5 December 2017, the case was reassigned to Special Master Oler. Notice of Reassignment, ECF No. 59. Petitioners filed additional medical records on 6 March 2018. Medical Records. The government filed a supplement expert report from Dr. Barañano and an expert report from Dr. Stephen McGeady with supporting medical literature. Supplemental Barañano Expert Rep., ECF No. 67; First McGeady Rep. ECF No. 70; Medical Literature, ECF No. 71. The parties filed their pre-hearing submissions on 31 December 2019 and pre-hearing briefs along with additional medical literature on 8 January 2020. Resp't's Prehr'g Submissions, ECF No. 75; Pet'rs' Prehr'g Submissions, ECF No. 76; Pet'rs' Prehr'g Submissions, ECF No. 78; Pet'rs' Prehr'g Submissions, ECF No. 79; Resp't's Prehr'g Submissions, ECF No. 80; Medical Literature, ECF No. 81.

Special Master Oler held an entitlement hearing on 22 January 2020. *See* Entitlement Hr'g Tr., ECF No. 88. At the conclusion of the hearing, Special Master Oler requested the parties file several documents. *See* Scheduling Order of 29 January 2020, ECF No. 86. The Special Master also "informed . . . petitioners' counsel, that the record, as it currently stood, did not enable [p]etitioners to meet their burden" and "suggested . . . [p]etitioners retain[] an

additional expert neurologist." SM Dec. at 4 n.7. Petitioners retained Dr. Lawrence Steinman and filed the report from Dr. Steinman on 24 July 2020. *See* Pet'rs' Status Rep. of 14 April 2020 at 1, ECF No. 92; Steinman Rep., ECF No. 101. The government filed another expert report by Dr. McGeady on 1 December 2020. Second McGeady Rep., ECF No. 104. Dr. Steinman's reply was filed on 12 February 2021. Steinman Reply, ECF No. 108.

Petitioners filed a post-hearing brief on 15 May 2021. Pet'rs' Posthr'g Br., ECF No. 113. The government responded on 8 July 2021, and petitioners replied on 15 July 2021. Resp't Posthr'g Br., ECF No. 116; Pet'rs' Resp. to Posthr'g Br., ECF No. 118. The parties indicated the record was complete on 9 August 2021. *See* JSR at 1, ECF No. 119. The Special Master dismissed the petition on 14 April 2022. SM Dec. at 74.

In her decision on entitlement, the Special Master summarized the procedural history of the case, the medical records of H.H., the affidavits and testimony of the fact witnesses, and the qualifications, reports, and testimony of the parties' experts. *Id.* at 1–45. The Special Master then explained the applicable law for an off-table injury (one not included in the Vaccine Injury Table under the Vaccine Act § 11(c)(1)(C)(ii)), including each prong of the three-part *Althen* analysis used for direct causation, and each prong of the six-part *Loving* analysis, used for significant aggravation claims, and the relevant standards for assessing evidence. *Id.* at 45–50. The Special Master began the analysis section of her decision by making the preliminary determination "H.H. has Aicardi-Goutières syndrome or a [s]imilar [t]ype I [i]nterferonopathy due to a [c]ongenital [a]bnormality in an [u]nidentified [g]ene." *Id.* at 50. In determining this diagnosis, the Special Master reviewed several factors: (1) clinical presentation; (2) elevated liver enzymes; (3) elevated interferon alpha/neopterin levels; (4) genetic mutation; (5) calcifications; (6) basal ganglia damage; (7) normalization of neopterin levels; (8) onset of AGS after 12 months; and (9) neurological stabilization and improvement. *See id.* at 50–60.

The Special Master credited the many treating physicians who found "H.H[.]'s clinical presentation was suggestive of or consistent with AGS." *Id.* at 52–53 ("Dr. Aalbers . . . noted . . . H.H[.]'s [symptoms] . . . were all consistent with AGS.") ("Dr. Heather Crawford . . . . noted . . . H.H. presented with developmental regression and developed progressive dystonia that is characteristic of [AGS].") ("Dr. Vanderver indicated an intent to collaborate with Dr. Crow to facilitate genetic resolution of suspected heritable interferonopathy."). The Special Master also relied on the opinion of Dr. McGeady, the government's expert, who opined H.H. had "evidence of leukodystrophy and thinning of the corpus callosum, which are described in AGS." SM Dec. at 52 (citing First McGeady Rep. at 4).

The Special Master highlighted the Rice paper, a 2007 study of 123 patients with a confirmed AGS gene mutation, as supporting Dr. McGeady's opinion of liver enzymes favoring a diagnosis of AGS, and accordingly found H.H.'s elevated liver enzymes supported a diagnosis of AGS. *See id.* at 53. Additionally, the Special Master found H.H.'s elevated levels of neopterin and interferon alpha were diagnostic for AGS. *Id.* at 55 ("There was no explanation for H.H.'s elevated neopterin and interferon alpha levels other than AGS."). The Special Master relied on treating physicians, medical literature, and expert testimony to make the finding. *Id.* at 52–55.

The Special Master stated "[t]he fact . . . H.H. does not have a gene currently identified with AGS is [p]etitioners' strongest argument that he does not have the disease." *Id.* at 55. The Special Master also acknowledged "five percent of AGS cases are associated with an unidentified genetic mutation." *Id.* (citing Barañano Rep. at 1). The Special Master did not believe the lack of a genetic mutation or "'major characteristics' that have been observed in other patients with AGS" excluded an AGS diagnosis. SM Dec. at 55. Relying on the 2015 Crow & Manel study, which discusses the molecular and cellular basis of interferonopathies, their categorization, future treatment strategies, and the insights they provide into normal physiology, the Special Master reasoned "'the range of phenotypes associated with mutations' or AGS genes 'is much broader than previously realized' [and] patients 'frequently lack one or more, *sometimes even all*, of the original diagnostic criteria.'" *Id.* (citing Crow & Manel, *Aicardi-Goutières syndrome and the type I interferonopathies*, 15 NATURE REVIEWS IMMUNOLOGY 429, 429 (2015), ECF No. 70-1 [hereinafter *Crow & Manel*].

Petitioners argued "H.H. does not exhibit four other 'major characteristics' so the Special Master addresses those characteristics in turn. *Id.* H.H. did not have calcifications, but the Special Master, replying on Dr. Barañano and Dr. McGeady's testimonies, determined calcifications were not required for a AGS diagnosis. *Id.* at 56. Considering damage to the basal ganglia, a group of subcortical nuclei responsible primarily for motor control, the Special Master determined "basal ganglia damage [was not] a major characteristic of AGS." *Id.* at 57. The Special Master reasoned Crow & Manel did not list basal ganglia damage as a major characteristic. *Id.* at 56. The government's expert, Dr. Barañano, testified basal ganglia damage may be seen in AGS cases with an adenosine deaminase acting on ribonucleic acid ("ADAR") mutation, but it is not universally seen in all AGS cases. SM Dec. at 57. Accordingly, the Special Master found basal ganglia damage to not be a major characteristic of AGS and the lack of basal ganglia damage did not eliminate an AGS diagnosis. *Id.*

Petitioners asserted the normalization of neopterin levels is characteristic of AGS; the Special Master disagreed. *Id.* at 58. The Special Master found the "medical literature . . . does not provide compelling support for the point that it is characteristic for AGS patients to experience normalization in neopterin level." *Id.* at 57. The Special Master points out petitioners' expert, Dr. Marks, initially favored vaccine causation over AGS because of the normalization in neopterin levels but reversed his position when the levels elevated again.[2] *Id.*

The Special Master determined the fact "H.H. developed symptoms consistent with AGS at 15 months . . . does not provide persuasive evidence that H.H. does not have AGS, as cases of later onset are reported in the medical literature." *Id.* at 58. Various medical studies support the notion "there is variability in AGS presentation which includes onset after the first year of life." SM Dec. at 58. Further, Drs. McGeady and Barañano also testified of the variability of onset. *See id.*

In their post-hearing brief, H.H.'s treating physician, Dr. Marks, asserted neurological improvement and stabilization supported a non-AGS diagnosis. *Id.* at 59. The Special Master disagreed and found the medical literature supported the opinions of the government's experts, Drs. McGeady and Barañano, who opined "AGS is not necessarily a 'relentlessly progressive

[2] At oral argument, petitioners asserted Dr. Marks still believes H.H.'s injury is vaccine-caused. Tr. at 24:2–3.

neurogenerative disorder'" and can have a "'period of stabilization.'" *Id.* (quoting Entitlement Hr'g Tr. at 270:8, 10–11). The Special Master found the stabilization of H.H.'s condition supported a diagnosis of AGS. *Id.* at 71.

Following the diagnosis of an AGS or AGS-like disorder, the Special Master determined the injury manifested around the time of the 17 October 2013 vaccination and before the 23 October 2013 vaccination. *Id.* at 60. The Special Master found there was not preponderant evidence to support an onset in September of 2013 because there was not sufficient evidence to draw a conclusion, and "none of the experts explained why or how H.H. would begin to demonstrate signs of his genetic disorder and then improve." SM Dec. at 60. While the Special Master did not find evidence to support onset in September of 2013, the Special Master did find evidence for onset of symptoms after the administration of the influenza and pneumonia vaccines but before the Pentacel vaccination. *Id.* at 62. The Special Master relied on contemporaneous medical records from 11 November 2013, which indicated H.H.'s "development ha[d] regressed in the last month," placing the start of regression prior to the vaccinations. *Id.* at 61. The Special Master considered the testimony of several fact witnesses who also testified on H.H.'s right cord tightness, foot dragging, and falling prior to the 23 October 2013 Pentacel vaccination. *Id.* at 61–63.

After determining a diagnosis and narrowing the issue to whether the Pentacel vaccine significantly aggravated H.H.'s condition, the Special Master began the six-part *Loving* analysis, used to determine if a vaccine significantly aggravated H.H.'s injury. *Id.* at 63. For *Loving* prongs one and two, which look at the condition prior to and following the administration of a vaccination, the Special Master concisely described H.H.'s condition before and after the 23 October 2013 vaccination. *Id.* In prong three of *Loving*, which compares the conditions before and after the administration of a vaccination, the Special Master found the deterioration in H.H. was "consistent with the Vaccine Act's definition of significant aggravation resulting in markedly greater disability, pain, or illness accompanied by substantial deterioration of health." *Id.* The Special Master then turned to the question of whether the significant aggravation of H.H.'s condition was vaccine-related. SM Dec. at 63.

For *Loving* prong four, which requires a reputable medical explanation demonstrating the vaccine received can cause the type of injury alleged, the Special Master concluded petitioners did not establish a reliable and reputable theory. *Id.* at 67–68. The Special Master analyzed petitioners' expert Dr. Steinman's proposed medical theory who opined the "Pentacel vaccine activated H.H.'s immune system resulting in the production of type I and II interferons, which led to the worsening of his neuroinflammation." *Id.* at 65. The Special Master then reviewed the medical literature used to support Dr. Steinman's theory. *Id.* The literature supported the notion "vaccines may activate the inflammasome," but the Special Master found "Dr. Steinman ha[d] not presented a link between such activation and the development of AGS or a similar type I interferonopathy." *Id.* at 66. Further, the Special Master credited the government's expert, Dr. McGeady, and reasoned petitioners' theory did not explain how the vaccinations caused the "massively exaggerated" levels of interferon alpha or explain how the levels remained elevated for years after vaccination. *Id.* (internal quotations omitted).

Regarding *Loving* prong five, which requires a logical sequence of cause and effect

between the administration of a vaccination and the significant aggravation of a condition, the Special Master found petitioners neither provided evidence demonstrating H.H. experienced a vaccine-associated significant aggravation of his interferonopathy nor furnished support for the theory vaccines H.H. received affected his condition. SM Dec. at 68. First, the Special Master determined petitioners did not present evidence of direct causation because physical signs appeared prior to or at the same time as the 17 October vaccinations. *Id.* Next, the Special Master considered the medical records and determined the medical records supported finding the vaccine did not cause or significantly aggravate H.H.'s condition. *Id.* Specifically, the Special Master points to the lack of a local reaction at the time of vaccination and the presence of elevated transaminase levels. *Id.* at 68–69. The Special Master then evaluated whether the opinions of the treating physicians, Drs. Hollis and Marks, supported a logical sequence. *Id.* at 69. While the treating physicians opined H.H.'s injury was vaccine caused or aggravated, the Special Master discredited the opinions because neither expert was able to "articulate a causation theory." *Id.* at 69–72.

Finally, the Special Master considered *Loving* prong six, which requires the establishment of a proximate temporal relationship between the significant aggravation of a condition and the received vaccinations, and found petitioners did not offer "'preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology . . . is medically acceptable to infer causation.'" SM Dec. at 72 (quoting *de Bazan v. Sec'y of Health & Hum. Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008)). The Special Master disvalued Dr. Steinman's report finding H.H.'s disease course began three weeks after his receipt of the Pentacel vaccine because Dr. Steinman did not think there were real signs of H.H.'s interferonopathy prior to the vaccinations. *Id.* at 72. Further, the Special Master analyzed each piece of medical literature Dr. Steinman used to establish an onset time and discredited them. *Id.* at 73. Regarding the Schonberger, Bennetto, and Scolding articles, research studies used to support an injury onset of three weeks, the Special Master found the evidence unpersuasive because the articles dealt with different conditions with different underlying mechanisms than those presented by petitioners. *Id.* at 73–74. Accordingly, the Special Master found petitioners did not preponderantly establish a three-week onset as a medically acceptable onset interval. *Id.* at 74.

In conclusion, the Special Master found petitioners could not establish causation under any avenue. As such, the Special Master dismissed the petition. *Id.* On 16 May 2022, petitioners moved for review of the Special Master's decision dismissing the petition. Mot. for Review. The government filed its brief on 15 June 2022. Resp't's Resp., ECF No. 127. The Court now reviews the Special Master's decision.

III. Petitioners' Motion for Review and the Government's Arguments

On 16 May 2022, petitioners filed a motion for review of the Special Master's decision denying entitlement with an accompanying memorandum of law. *See* Mot. for Review; Mot. for Review Mem. Petitioners allege the Special Master erred in three ways: the Special Master (1) "improperly diagnos[ed p]etitioner with AGS or another genetically caused [t]ype [sic] I interferonopathy"; (2) "fail[ed] to recognize [p]etitioners' expert medically sound theory of causation of injury"; and (3) "improperly increased the burden of proof . . . for establishing the

logical sequence . . . and establishment of a temporal relationship . . . and devalued the expert opinion of [p]etitioners' [sic] expert." *Id.* at 1, 17–18. The Court will divide petitioners' third objection into *Loving* prongs five and six, as the government did in its response. *See* Resp't's Resp. at 10–12.

A. The Special Master's Diagnosis of AGS

Petitioners argue "the [d]ecision denying entitlement . . . rests largely with the [S]pecial [M]aster diagnosing . . . H.H. with AGS or some other unknown genetic Type I interferonopathy." Mot. for Review Mem. at 13. While petitioners do not "contest that H.H.'s injury is 'AGS-like,'" petitioners assert the Special Master erred by "improperly characteriz[ing] the meaning of 'AGS-like' to suggest that [p]etitioners' expert, Dr. Steinman was agreeing that 'AGS-like' meant that H.H. had a genetic interferonopathy" rather than a type I interferonopathy caused by the October 2013 vaccinations. *Id.* at 14.

Petitioners assert their "almost impossib[le] H.H. has AGS based off of the known medical statistics of the major characteristics of AGS." *Id.* Petitioners argue Dr. Steinman testified "there is no evidence or the probability is extremely low that H.H. has AGS or some unk[n]own gen[e]tic AGS[-]like disease based off the medical records and based off the leading experts in the world regarding AGS not having been able to diagnose him with the disease." *Id.* Petitioners argue the Special Master even recognized the low probability of H.H. having AGS or some unknown genetic AGS-like disorder. *See id.* at 14–15 ("[I]n 5% of AGS cases, there are no recognized genetic mutation, which would include H.H. Additionally, in 18% of AGS cases, there's normal development until symptom onset, which would include [p]etitioner. Also, in 8.6% of the AGS cases, development happens after 12 months, again, which includes [p]etitioner, and then in 25% of cases 'there is normalization of neopterin levels, and then in some other percent of cases, there are no calcifications."). Petitioners indicate the Special Master acknowledged "'a fair number of absences' that are not consistent with an AGS diagnosis" stating, "when you take all of those numbers and look at them together—and I'm not saying I'm making a decision based on the numbers[, b]ut when you take all those numbers and look at them together, this really seems like well beyond *one in a million . . . . it seems like an exceedingly rare instance.*" *Id.* at 15 (citing Entitlement Hr'g Tr. 290:9–291:15). Petitioners assert "despite the absolutely near impossibility" the Special Master "went against the great weight of evidence presented . . . and diagnosed [p]etitioner with 'more likely than not' AGS or a similar generic disorder, with a complete unknown etiology." *Id.* Petitioners further assert the government did not provide any medical evidence alleging the vaccinations "could not have caused his injury and only provided evidence that they are not aware of any [medical evidence] at this time, and therefore default to a differential diagnosis." *Id*.

The government disagrees, stating the Special Master "thoroughly reviewed the evidence" when the Special Master "considered [H.H.'s] clinical presentation, elevated liver enzymes, elevated interferon alpha/neopterin levels, and more, found persuasive the opinions of Drs. Barañano and McGeady, considered the notations in the medical records, and weighed the medical literature" to determine that "H.H[.]'s condition was consistent with a diagnosis of AGS or an AGS-like genetic condition." Resp't's Resp. at 13 (cleaned up). The government argues the "Special Master's conclusion . . . is well-supported by both expert opinion and the medical

records[.]" *Id.* ("In sum, she thoroughly reviewed the evidence and explained her reasoning, and her findings should not be disturbed."). The government indicates the "Special Master discussed at length the qualification of each expert witness, the testimony of each, and the field of medical literature submitted by both parties," and, therefore, the Special Master's "factual findings should be given the discretion they are entitled to." *Id.* at 13–14. The government further argues the diagnosis, even if erroneous, would not be fatal to the decision because petitioners "failed to meet their burden under any of the three *Althen* prongs [or *Loving* prongs 5 and 6]," which establishes causation in fact when the petitioner proves all three *Althen* prongs, and "failure to meet their burden under even one is dispositive and fatal to their case." *Id.* at 14.

B. *Loving* Prong Four/*Althen* Prong One: A Medical Theory Causally Connecting the Vaccination and the Injury

Petitioners argue in their second objection the Special Master "fail[ed] to recognize [p]etitioners' expert medically sound theory of causation of injury." Mot. for Review Mem. at 1. Citing *Althen*, petitioners argue circumstantial evidence can be used to meet the preponderance standard in a "field bereft of complete and direct proof of how vaccines affect the human body." *Id.* at 16 (quoting *Althen v. Sec'y of Health & Hum. Servs.*, 418 F.3d 1274, 1280 (Fed. Cir. 2005)). Petitioners assert they "provided a medical theory, albeit in an area bereft of medical literature and knowledge of the mechanism of injury that [p]etitioner[s'] interferonopathy was caused or substantially aggravated by the vaccines H.H. received, and that H.H. does not have AGS or a similar unknown genetic injury." *Id.* Petitioners argue "Dr. Steinman, produced med[ical] literature that supports his theory that [v]accinations can cause the production of interferon," and, in turn, "experts agree that overproduction or an excessive amount of interferons can cause the type of injury seen in [H.H.]." *Id.* Petitioners continue, Dr. Steinman "offered testimony that interferon response was absent or deficient in H.H. and as a result his immune system continuously produced type I interfe[ron], which resulted in the disease." *Id.* at 17.

Petitioners argue the Special Master's decision improperly required petitioners to "produce either testimony or medical literature to state that in this particular case, the vaccines did not cause [H.H.] to overproduce interferons." *Id.* Additionally, petitioners argue they had to "prove that the vaccinations of October 2013 could cause [interferon] production and that the [interferons] produced to a level that caused grave injury[—]the injury being one that resembles a genetic disease . . . but only a scintilla of evidence suggests that H.H.'s injury is caused by genetic mutation." Mot. for Review Mem. at 17. Petitioners assert the government's expert did not "provide any evidence that the vaccinations could not have caused his injury" but has "only provided testimony from non-treating physicians that opine[d] they are not aware of any medical literature or cases where a vaccination caused an "AGS-[l]ike" interferonopathy." *Id.* at 15–16. Under *Althen*, petitioners argue, the issue of "whether H.H. has AGS and if a vaccine could cause it" is a "close call" and should be resolved in favor of petitioners. *Id.* at 1, 16 (citing *Althen*, 418 F.3d at 1280).

The government argues petitioners "failed to establish a reliable and reputable theory" or "reliable evidence in support of the[] theor[y]." Resp't's Resp. at 6, 8. The government asserts *Althen* prong one requires "a medical theory be 'persuasive'—that is, a specific to petitioners'

case and supported by a 'reputable' (i.e., reliable) scientific or medical explanation." *Id.* at 5 (citing *Moberly v. Health & Hum. Servs.*, 592 F.3d 1315, 1322 (Fed. Cir. 2010)). *See Boatmon v. Sec'y of Health & Hum. Servs*., 941 F.3d 1351, 1360 (Fed. Cir. 2019) (rejecting "likely caused," "plausible," or "possible" causal theories). The government asserts it is in the Special Master's purview to reject—as the Special Master did— "an expert's conclusion 'connected to existing data only by the *ipse dixit* of the expert,' especially if 'there is simply too great an analytical gap between the data and the opinion proffered.'" *Id.* at 8 (quoting *Snyder v. Sec'y of Health & Hum. Servs.*, 88 Fed. Cl. 706, 743 (2009)). Additionally, the government contends the Special Master "carefully considered the qualifications, written reports, and testimony of all the experts, as well as the literature, and appropriately determined petitioners' theory was not supported by a reputable scientific explanation." *Id.* Specifically, the government agrees with the Special Master's conclusion regarding "one of the articles upon which Dr. Steinman heavily relied" to show vaccinations may trigger a interferonopathy "does not provide persuasive evidence in support of [p]etitioners' theory in this case." *Id.* at 8. The government further asserts petitioners "provided a wholly speculative theory that was not supported by the scientific research," and even if petitioners "had provided sufficient evidence to establish that Dr. Steinman's theory was possible, that would not have been sufficient to meet their burden." *Id.* at 10. Additionally, the government argues petitioners' characterization of causation as a "close call" indicates the legal insufficiency and lack of reliable and reputable evidence to support the causation. *Id.* at 9–10.

C. *Loving* Prong Five/*Althen* Prong Two: A Logical Sequence of Cause and Effect Showing the Vaccination was the Reason for the Injury

Petitioners' third objection, in part, relates to the Special Master's analysis of the logical sequence of cause and effect between the administration of the vaccination and the manifestation of the injury. Mot. for Review Mem. at 17 ("The [d]ecision improperly increased the burden of proof past the preponderance of the evidence standard for establishing a logical sequence of cause and effect."). Petitioners allege the Special Master "devalued . . . [the p]etitioners' expert" who "provided evidence sufficient to satisfy [p]rongs 5 and 6 of *Loving* when discussing whether the Pentacel vaccination significantly aggravated H.H.'s injury, which would also satisfy *Althen*." *Id.* at 19. Citing the Federal Circuit, petitioners further assert "the question of whether an expert's theory has been subjected to peer review and publication is not determinative of an expert's reliability" nor should an expert's opinions on causation be "held to the standard of scientific certainty" or "viewed through the lens of the laboratorian." *Id.* at 18 (first quoting *Boatmon*, 941 F.3d at 1359; then quoting *Andreu ex rel. Andreu v. Sec'y of Health & Hum. Servs.*, 569 F.3d 1367, 1380 (Fed. Cir. 2009)). By devaluing expert opinion, petitioners argue the Special Master increased the burden of proof for petitioners. *Id.* at 18.

The government maintains, as the Special Master concluded, "H.H[.]'s deterioration . . . close-in-time to his vaccination" and the mere fact "no other explanation exists" is insufficient to show the vaccines caused a significant aggravation of H.H.'s condition. Resp't's Resp. at 11. The government, citing *Moberly*, argues petitioners did not meet the burden of showing actual causation because a proximate temporal relationship between vaccine and injury is insufficient. *Id.* at 11 (citing *Moberly ex rel. Moberly v. Sec'y of Health & Hum. Servs.*, 592 F.3d 1315, 1323 (Fed. Cir. 2010) (holding "mere showing of a proximate temporal relationship

between vaccine and injury, nor a simplistic elimination of other potential causes of injury suffices")).

D. *Loving* Prong Six/*Althen* Prong Three: A Showing of a Proximate Temporal Relationship Between Vaccination and the Injury

Petitioners assert in the second half of their third objection the Special Master "increased the burden of proof . . . to prove the theory that H.H. was a healthy child prior to his October 2013 vaccinations, and with three weeks of those vaccinations, he was a severely and permanently injured child." Mot. to Review Mem. at 18. Petitioners argue they met their burden of proof because "'the proximate temporal relationship prong requires preponderant proof that the onset of symptoms occurred with a timeframe for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact.'" *Id.* (quoting *de Bazan v. Sec'y of Health & Hum. Servs.*, 529 F.3d 1347, 1352 (Fed. Cir. 2008)). Petitioners argue Dr. Steinman, petitioners' expert, "concisely and with supporting medical literature provided evidence sufficient to satisfy prong[s] 5 and 6 of *Loving* . . . which would also satisfy *Althen*." *Id.* Petitioners argue the Special Master erroneously dismissed its expert's testimony showing temporal causation. *Id.*

The government asserts the Special Master was correct in finding petitioners unable to establish a proximate temporal relationship regarding the significant aggravation claim. Resp't's Resp. at 12, 12 n.4. The government argues—and the Special Master found—petitioner did not establish a medically acceptable timeline from which to infer causation. *Id.* The temporal relationship analysis "necessarily intersects with the prong one analysis (providing a reliable medical theory causally connecting the resulting condition to the received vaccinations)," and therefore, the government argues, petitioners could not have met their burden because they did not present a reliable medical theory related to the "onset or worsening of the disease." *Id.* at 11. The government further argues the Special Master's decision was "well-support[ed] by evidence" and well-reasoned as the Special Master "carefully considered the qualifications, written reports, and testimony of all the experts, as well as the literature." *Id.* at 12, 8. Specifically, the government agrees with the Special Master's finding an article related to the onset of GBS after swine flu vaccination was used in support of petitioners' timing argument, unpersuasive because the vaccination, injury, and theory of causation were not analogous. *Id.* at 12, 12 n.5.

IV. Legal Standards

A. The Court's Standard of Review of a Special Master's Decision

The Vaccine Act provides this Court jurisdiction to review a special master's decision upon timely motion of either party. *See* 42 U.S.C. § 300aa-12I(1)–(2) (2018). In reviewing the record of the proceedings before the special master, the Court may: (1) "uphold the findings of fact and conclusions of law of the special master and sustain the special master's decision"; (2) "set aside any findings of fact or conclusion of law of the special master found to be arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law and issue its own findings of fact and conclusions of law"; or (3) "remand the petition to the special master for

further action in accordance with the court's direction." *Id.* at § 300aa-12(e)(2). "Fact findings are reviewed . . . under the arbitrary and capricious standard; legal questions under the 'not in accordance with law' standard; and discretionary rulings under the abuse of discretion standard." *Saunders v. Sec'y of Health & Hum. Servs.*, 25 F.3d 1031, 1033 (Fed. Cir. 1994) (quoting *Munn v. Sec'y of Health & Hum. Servs.*, 970 F.2d 863, 870 n.10 (Fed. Cir. 1992)).

It is not the Court's role "to reweigh the factual evidence, or to assess whether the special master correctly evaluated the evidence." *Lampe v. Sec'y of Health & Hum. Servs.*, 219 F.3d 1357, 1360 (Fed. Cir. 2000) (quoting *Munn*, 970 F.2d at 871). The Court also does "not examine the probative value of the evidence or the credibility of the witnesses." *Id.* These are all matters within the purview of the fact finder." *Id.* (quoting *Munn*, 970 F.2d at 871). "Reversal is appropriate only when the special master's decision is arbitrary, capricious, an abuse of discretion, or not in accordance with the law." *Snyder v. Sec'y of Health & Hum. Servs.*, 88 Fed. Cl. 706, 718 (2009). The arbitrary and capricious standard "is a highly deferential standard of review[:] [i]f the special master has considered the relevant evidence of record, drawn plausible inferences and articulated a rational basis for the decision, reversible error will be extremely difficult to demonstrate." *Hines ex rel. Sevier v. Sec'y of Health & Hum. Servs.*, 940 F.2d 1518, 1528 (Fed. Cir. 1991).

B. The Standard of Causation in Vaccine Cases

"A petitioner seeking compensation under the Vaccine Act must prove by a preponderance of the evidence that the injury or death at issue was caused by a vaccine." *Broekelschen v. Sec'y of Health & Hum. Servs*., 618 F.3d 1339, 1341 (Fed. Cir. 2010) (citing 42 U.S.C. §§ 300aa-11(c)(1), 300aa-13(a)(1)). "A petitioner can show causation under the Vaccine Act in one of two ways": (1) "by showing that she sustained an injury in association with a vaccine listed in the Vaccine Injury Table[,] . . . [i]n such a case, causation is presumed"; or (2) "if the complained-of injury is not listed in the Vaccine Injury Table . . . the petitioner may seek compensation by proving causation in fact." *Id.* at 1341–42 (internal citations omitted). Vaccine cases employ a burden shifting standard: "[o]nce the petitioner has demonstrated causation, she is entitled to compensation unless the government can show by a preponderance of the evidence that the injury is due to factors unrelated to the vaccine." *Id.* at 1342 (citing *Doe v. Sec'y of Health & Hum. Servs*., 601 F.3d 1349, 1351 (Fed. Cir. 2010)).

"For off-table claims (one not included in the Vaccine Injury Table under the Vaccine Act § 11(c)(1)(C)(ii)) that an injury was either 'sustained, or [] significantly aggravated,' a petitioner must show the vaccine 'caused' the injury or aggravation." *W.C. v. Sec'y of Health & Hum. Servs.*, 704 F.3d 1352, 1357 (Fed. Cir. 2013) (citing 42 U.S.C. § 300aa-11(c)(1)(C)(ii)). "When a petitioner has suffered an off-[t]able injury . . . [the Federal Circuit] has established the following test for showing causation in fact under the Vaccine Act:"

> [The petitioner's] burden is to show by preponderant evidence that the vaccination brought about her injury by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury.

Broekelschen, 618 F.3d at 1345 (quoting *Althen*, 418 F.3d at 1278). "A petitioner must prove by preponderant evidence that the vaccination caused significant aggravation by showing:"

> (1) the person's condition prior to administration of the vaccine, (2) the person's current condition (or the condition following the vaccination if that is also pertinent), (3) whether the person's current condition constitutes a "significant aggravation" of the person's condition prior to vaccination, (4) a medical theory causally connecting such a significantly worsened condition to the vaccination, (5) a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation, and (6) . . . a proximate temporal relationship between the vaccination and the significant aggravation.

W.C., 704 F.3d at 1357 (Fed. Cir. 2013) (citing *Loving ex rel. Loving v. Sec'y of Health & Hum. Servs.*, 86 Fed. Cl. 135, 144 (2005)). The Federal Circuit in *W.C.* espoused "[t]he *Loving* test combines the first three *Whitecotton* factors, which establish significant aggravation, with the *Althen* factors, which establish causation." *Id.* Accordingly, the standards for assessing *Althen* prongs 1–3 also apply to *Loving* prongs 4–6. *Id.*

Under the first prong of *Althen*, "[a] petitioner must provide a 'reputable medical or scientific explanation' for its theory." *Boatmon*, 941 F.3d at 1359 (quoting *Moberly*, 592 F.3d at 1322). "While it does not require medical or scientific certainty, [the explanation] must still be 'sound and reliable.'" *Id.* (quoting *Knudsen ex rel. Knudsen v. Sec'y of Health & Hum. Servs.*, 35 F.3d 543, 548–49 (Fed. Cir. 1994)). Petitioners "need not produce medical literature or epidemiological evidence to establish causation under the Vaccine Act." *Andreu ex rel. Andreu v. Sec'y of Health & Hum. Servs.*, 569 F.3d 1367, 1379 (Fed. Cir. 2009). Where such evidence is introduced, it must not be viewed "through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard" *Id.* at 1380. For satisfying the second *Althen* prong, "medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether 'a logical sequence of cause and effect show[s] that the vaccination was the reason for the injury.'" *Capizzano v. Sec'y of Health & Hum. Servs.*, 440 F.3d 1317, 1326 (Fed. Cir. 2006) (quoting *Althen*, 418 F.3d at 1280). Lastly, "the proximate temporal relationship prong requires preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." *de Bazan v. Sec'y of Health & Hum. Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008).

V. Review of the Special Master's Decision on Entitlement

Petitioners alleged H.H.'s injuries were caused or significantly aggravated by the influenza, pneumonia, and Pentacel vaccines, administered on 17 October 2013 and 23 October 2013, respectively. *See* Pet. at 1. The Special Master reviewed the record for each of the three vaccines as the cause or significant aggravation of H.H.'s injury. SM Dec. at 63 ("I am unable to make a specific finding as to whether H.H. began to develop signs of his type I interferonopathy before or after the flu and pneumonia vaccines, I have not analyzed whether these vaccines either caused or significantly aggravated H.H.'s condition."). In their memorandum regarding their

motion for review, petitioners alleged the Special Master erred in determining whether any of the three vaccines caused or significantly aggravated H.H.'s injury. Mot. for Review Mem. at 11, 18 ("[T]ype I interferonopathy [was] caused by the *vaccination[-]triggering event in October 2013*." (emphasis added)) (asserting the Special Master erred in applying *Loving* prongs 4, 5 & 6 for the significant aggravation analysis). Accordingly, the Court reviews the Special Master's decision to determine whether the Special Master erred in finding the influenza, pneumonia, and Pentacel vaccines did not cause or significantly aggravate H.H.'s type I interferonopathy.

A. The Special Master's Consideration of the Influenza and Pneumonia Vaccinations

As part of the Special Master's decision, the Special Master considered whether the influenza and pneumonia vaccines caused or significantly aggravated H.H.'s injury. SM Dec. at 63. The Special Master stated, "I have not analyzed whether [the influenza and pneumonia] vaccines either caused or significantly aggravated H.H.'s condition because Dr. Steinman only offered an opinion with respect to the Pentacel vaccine." *Id.* The Special Master did not analyze causation–in–fact for the influenza and pneumonia vaccinations because petitioners did not present evidence showing causation in fact for influenza and pneumonia. *Id.* Petitioners did not expressly object to this finding in their motion for review. *See* Mot. for Review Mem. at 1.

At oral argument, the parties disputed the scope of Dr. Steinman's report. *See* Tr., ECF No. 131. Under the Vaccine Act, petitioners seeking compensation "must prove by a preponderance of the evidence that the injury or death was caused by a vaccine." *Broekelschen v. Sec'y of Health & Hum. Servs*., 618 F.3d 1339, 1341 (Fed. Cir. 2010) (citing 42 U.S.C. §§ 300aa-11(c)(1), 300aa-13(a)(1)). At oral argument, the government posited "Dr. Steinman only addresses the Pentacel vaccine" and argued the discussion of the Special Master's decision should be limited to the findings related to Pentacel. Tr. at 13:12–15. Petitioners stated Dr. Steinman "did reference both sets of vaccinations having been causes of the injury" in generic terms, but Dr. Steinman "focus[ed] on Pentacel" when opining on the medical theory and causation in fact of H.H.'s injury. *Id.* at 37:18–21. After further questioning, petitioners conceded their "theory is that the Pentacel significantly aggravated his interferonopathy and caused it." *Id.* at 91:12–15. Specifically, petitioners did not provide a medical theory showing the influenza and/or pneumonia vaccines can cause interferonopathies. SM Dec. at 63 ("Dr. Steinman only offered an opinion with respect to the Pentacel vaccine."); Tr. at 37:18–21 ("THE COURT: [D]oes Dr. Steinman address all three vaccines? [PETITIONERS]: He addresses them . . . in a more general term, as the October 2013 vaccinations, including the flu vaccination and then Pentacel . . . so he did reference both sets of vaccinations and having been causes of the injury, but did then focus on Pentacel . . . ."), 38:1–3 ("THE COURT: [I]t's fair to say, that Dr. Steinman's report focuses on Pentacel? [PETITIONERS]: It does focus on Pentacel."). The parties both agree petitioners' expert, Dr. Steinman, focused on the medical theory related to the components contained in the Pentacel vaccine. *Id.* at 13:12–15, 37:18–21.

Petitioners seeking compensation "must prove by a preponderance of the evidence that the injury or death was caused by a vaccine." *Broekelschen*, 618 F.3d at 1341 (citing 42 U.S.C. §§ 300aa-11(c)(1), 300aa-13(a)(1)). The parties agree—and the Special Master found—Dr. Steinman did not opine on the influenza and pneumonia vaccines, and therefore did not put forth

evidence to show causation. *Id.* Accordingly, the Court finds the Special Master did not err in finding the influenza and pneumonia vaccines did not cause H.H.'s injury. *Id.*

B. The Special Master's Consideration of Direct Causation v. Significant Aggravation

There are two separate avenues to recovery under the Vaccine Act: a petitioner can allege a vaccine (1) caused a new injury; or (2) significantly aggravated an existing injury. *Loving*, 86 Fed. Cl. at 143. The Federal Circuit explained "vaccine-related injury or death" means "illness, injury, condition, [that] has to be more than just a symptom or manifestation of an unknown injury."[3] *Lombardi v. Sec'y of Health & Hum. Servs.*, 656 F.3d 1343, 1352 (citing *Broekelschen*, 618 F.3d at 1349). Two injuries—like a genetic injury and a vaccine-aggravated injury—can have overlapping symptoms. *See Broekelschen*, 618 F.3d at 1346 (observing the two disputed injuries, transverse myelitis and anterior spinal artery syndrome, had overlapping symptoms).

In this case, petitioners alleged entitlement under both avenues, so the Special Master considered whether the Pentacel vaccine caused or significantly aggravated H.H.'s injury. SM Dec. at 63. The Special Master found "the Pentacel vaccine did not [directly] cause H.H.'s condition" because "H.H. began to show signs of his type I interferonopathy before he received the Pentacel vaccine," and eliminated a direct causation analysis. *Id.* (citing *Locane v. Sec'y of Health & Hum. Servs.*, 685 F.3d 1375, 1381 (Fed. Cir. 2012)). The Special Master found "H.H. began to develop heel cord tightness around the time he received his October 17, 2013 vaccinations, and before the received the Pentacel vaccine, and further that this heel cord tightness constituted a physical sign of his type I interferonopathy." *Id.* at 72. Accordingly, the Special Master focused on the significant aggravation of H.H.'s injury. *Id.* at 63 ("My finding . . . makes the analysis more pointed. It . . . raises the question as to whether the Pentacel vaccine caused the significant aggravation of H.H.'s genetic condition that had already begun to manifest.").

The parties dispute whether petitioners allege a direct causation theory or a significant aggravation theory on review. In their memorandum regarding their motion for review, petitioners stated H.H.'s "interferonopathy was caused or substantially aggravated" by the vaccinations received. Mot. for Review Mem. at 16. The government argued petitioners only focus on a significant aggravation theory because "[p]etitioners did not raise any legal challenges" to the Special Master's factual finding physical signs of interferonopathy—heel cord tightening—around October 17, 2013. Resp't's Resp. at 12 n.4; Tr. at 91:5–15 ([PETITIONERS]: [W]e did not specifically address her fact finding in [] our motion for review."). By not challenging the factual finding, the government suggests petitioners' motion for review and memorandum regarding their motion to review "assumes that the case involves the significant aggravation of their son's pre-existing condition." *See* Resp't's Resp. at 12, 12 n.4.

[3] The Special Master in her decision uses "diagnosis," "disorder," and "condition" terminology interchangeably with injury.

During oral argument, both parties agreed with the Special Master in finding the onset of symptoms were sometime between 17 October 2013 and 23 October 2013. Tr. at 90:1–19. At the beginning of oral argument, petitioners generally maintained "the injury was caused by the vaccination, causing a type I interferonopathy." *Id.* at 8:10–22. If the injury was not caused by vaccine, petitioners alternatively asserted, "a genetic type I interferonopathy, an unknown genetic type I interferonopathy . . . was significantly aggravated by the vaccinations." *Id.* Regarding timing, petitioners recognized at the 13 October 2013 flu vaccinations appointment, "there were signs that he . . . began to have overactive interferons." *Id.* at 90:11-16. Petitioners conceded the manifestation of physical signs around the 13 October 2013 vaccinations appointment points to significant aggravation as the primary theory. *Id.* at 90:20–22 ("[PETITIONERS]: It is petitioners' belief . . . [at] the October 13th flu vaccination . . . there were signs . . . that he began to have overactive interferons . . . that puts us into the significantly aggravated case or area of law."). While petitioners did not "want to take the complete causation theory off the table," they acknowledged "Dr. Steinman just opined in his expert report, focusing on a significant aggravation theory." *Id.* at 91:2–9 ("THE COURT: [A]re petitioners still making a complete causation theory? [PETITIONERS]: I don't want to take the complete causation theory off the table, but our expert witnesses relied and testified—well Dr. Steinman just opined in his expert report, focusing on a significant aggravation theory. [E]specially with the Special Master's fact-finding, we did not specifically address her fact-finding in . . . our motion for review."). Consequently, as petitioners stated, "evidence of a slight heel cord tightening" favors "Pentacel significantly aggravating [H.H.'s] interferonopathy" as petitioners' primary theory. Tr. at 90:20–22, 91:10–15 ("[PETITIONERS]: There was evidence of a slight heel cord tightening, so petitioners' theory is that the Pentacel significantly aggravated his interferonopathy and caused it.").

In this case, the Special Master found "preponderant evidence that the onset of H.H.'s condition began close-in-time to his October 17, 2013 vaccinations and before he received the Pentacel vaccine." SM Dec. at 63. The Special Master relied on contemporaneous medical records from 11 November 2013, which indicated H.H.'s "development ha[d] regressed in the last month," placing the start of regression prior to the vaccinations. *Id.* at 61. The Special Master considered the testimony of several fact witnesses who also testified about H.H.'s right cord tightness, foot dragging, and falling prior to the 23 October 2013 Pentacel vaccine. *Id.* at 61–63. Given all the evidence, the Special Master found "H.H. began to show signs of his type I interferonopathy *before* he received the Pentacel vaccine." *Id.* at 63 (emphasis added). As petitioners raised no allegation of error in the Special Master's factual finding, the Court does not review the finding for error.

Evidence of physical symptoms prior to vaccination eliminates a direct causation claim. *Locane*, 685 F.3d at 1381 ("[I]f the illness was present before the vaccine was administered, logically, the vaccine could not have caused the illness."). The Special Master found "H.H. began to develop heel cord tightness around the time he received his 17 October 2013 vaccinations[] and before he received the Pentacel vaccine, and . . . this heel cord tightness constituted a physical sign of his type I interferonopathy," which eliminates the possibility of the vaccine directly causing H.H.'s injury. SM Dec. at 63 (citing *Locane*, 685 F.3d at 1381). Petitioners' expert Dr. Steinman could not account for the early symptoms stemming from

H.H.'s genetic injury in his direct causation theory.[4] Tr. at 91:2–9 ([PETITONERS]: "Dr. Steinman . . . focus[ed] on a significant aggravation theory."). The parties do not dispute the Special Master's factual finding of physical symptoms manifesting prior to administration of the Pentacel vaccine and therefore agree the finding eliminates a direct causation theory. Tr. at 90:20–22. Accordingly, the Court finds the Special Master did not err in only analyzing a significant aggravation theory for Pentacel because the physical symptoms of H.H.'s genetic injury appeared before his Pentacel vaccination. *See Locane*, 685 F.3d at 1381(stating if "the illness was present before the vaccine was administered, logically, the vaccine could not have caused the illness").

VI. The Special Master's Determination of Genetically Caused AGS or AGS-like Type I Interferonopathy

Before Special Master Oler analyzed whether the Pentacel vaccine could have significantly aggravated H.H.'s injury, the Special Master determined the record best supported an AGS or AGS-like type I interferonopathy injury. SM Dec. at 50–63. Petitioners first object to the Special Master "improperly diagnosing [H.H.] with AGS or another genetically caused [type] [sic] I interferonopathy[.]" Mot. for Review Mem. at 1. The Court will review the Special Master's decision as it relates to petitioners' theory of significant aggravation of H.H.'s injury by the Pentacel vaccine by first determining whether the Special Master erred in her diagnosis of AGS or AGS-like type I interferonopathy.

A. Whether the Special Master was Required to Diagnose

The Special Master's diagnosis is central to the parties' dispute in this case. The Special Master "found the evidence preponderantly supports the fact that H.H. has a genetic type I interferonopathy that is either AGS or is AGS-like." SM Dec. at 63. Petitioners object to the finding because it "improperly mischaracterized the meaning of 'AGS-like' to suggest . . . H.H. had a genetic [t]ype I [i]nterferonopathy as opposed to the October 2013 vaccinations causing the [t]ype I [i]nterferonopathy." Mot. for Review Mem. at 14. The government disagrees the Special Master erred in the diagnosis and further asserts, even if the "diagnosis was erroneous, such error would be harmless" because petitioners "failed to meet their burden under any of the three *Althen* prongs," which is "dispositive and fatal to their case." Resp't's Resp. at 14.

Before the Court can assess whether the Special Master mischaracterized the diagnosis, it must determine whether a diagnosis was allowed. Causation frameworks are determined

[4] Dr. Steinman opined on both an onset theory and a significant aggravation theory. *See* Steinman Rep. at 15–16. The Special Master found Dr. Steinman's opinion supporting an onset claim contrary to her findings of physical signs prior to the Pentacel vaccine. SM Dec. at 72 ("[M]y determination in this case is contrary to Dr. Steinman's."). Dr. Steinman did not believe "H.H. had pre-existing evidence of a neurological problem, unless the turning of the right foot inward was the earliest manifestation of dystonia." Steinman Rep. at 5. Dr. Steinman's report, however, acknowledges early physical signs but does not believe those were neurological signs. *Id.* Accordingly, he does not address how an onset theory accounts for them directly. Steinman Rep. at 8 ("Based on the records, I conclude that this is an interferonopathy with precious little evidence of any neurologic findings prior to the immunizations in October 2013."). In his reply, Dr. Steinman asserts "even if there was an underlying AGS condition in play in H.H., my logic is that the immunization would have worsened neuroinflammation in H.H." Steinman Reply at 3.

"relative to the injury." *Broekelschen v. Sec'y of Health & Hum. Servs.*, 618 F.3d 1339, 1346 (Fed. Cir. 2010). Accordingly, a special master may "first determine which injury was best supported by the evidence presented in the record *before* applying the *Althen* test[.]" *Id.* (emphasis added). In this case, the Special Master relied on *Broekelschen* to justify diagnosing H.H. prior to any causation analysis and found "in considering the evidence . . . . H.H., more likely than not, has AGS or a similar genetic interferonopathy." SM Dec. at 50, 60. In *Broekelschen*, the petitioner presented symptoms characteristics of two distinct diagnoses. *Broekelschen*, 618 F.3d at 1343. Each diagnosis had a predetermined cause. *Id.* at 1346 ("Transverse myelitis is an inflammatory event caused by an immune response, whereas anterior spinal artery syndrome is a vascular event caused by a blockage."). The Federal Circuit explained "nearly all of the evidence on causation was dependent on the diagnosis" and "because the injury itself [was] in dispute, the proposed injuries differ[ed] significantly in their pathology, and the question of causation turn[ed] on which injury [petitioner] suffered." *Id.* The Federal Circuit held "it was appropriate . . . for the special master to first determine which injury was best supported by the evidence presented in the record before applying the *Althen* test so that the special master could subsequently determine causation relative to the injury." *Id.* In *Broekelschen*, a causation analysis could not proceed without defining an injury, so the special master had to define the injury. *See id.*

In contrast, the parties in *Andreu* agreed the petitioner suffered from a seizure disorder but disputed whether an initial seizure was febrile or afebrile. *Andreu ex rel. Andreu v. Sec'y of Health & Hum. Servs.*, 569 F.3d 1367, 1378 (Fed. Cir. 2009). The Federal Circuit suggested the exact diagnosis or injury was not required to determine whether the vaccine caused the petitioner's injury because both parties agreed "whatever caused [petitioner's] first seizure also led to his subsequent seizure disorder." *Id.* at 1381. The question of whether the seizure was febrile or afebrile did "not change [the dispute] that the catalyst . . . was the . . . vaccine . . . [,]" and, similarly, the dispute in this case was not whether H.H. had an interferonopathy but whether "the October 2013 vaccinations caus[ed] the [t]ype I [i]nterferonopathy." *Id.* at 1378; Mot. for Review Mem. at 14. If the special master in *Andreu* had provided a diagnosis, narrowing the petitioner's injury to afebrile or febrile, the causation analysis would remain unchanged because the question was still if the vaccine caused the injury. In other words, an exact diagnosis was not needed to move forward with a causation analysis like it was in *Broekelschen*. *See Andreu*, 569 F.3d at 1378.

The preliminary question before the Court can address the diagnosis itself is whether the Special Master's diagnosis was permitted under *Andreu.* In this case, the parties do not dispute the injury—type I interferonopathy—is an inherited genetic disorder.[5] Tr. 28:15–17 ("[THE GOVERNMENT]: [M]y understanding is it's an interferonopathy[.]"), 29:25 ("[PETITIONERS]: The injury is an interferonopathy."). Instead, the parties dispute the underlying cause of the interferonopathy and whether the vaccine aggravated the injury. *Id.* at 10:14–19 ("THE COURT: [I]s it fair to say that the primary dispute here is the underlying cause of the injury, whether it was genetic or vaccine? [PETITIONERS]: The underlying

[5] Type I interferonopathies are a group of "monogenic diseases in which a constitutive upregulation of type I [interferon] production is considered directly relevant to pathogenesis." SM Dec. at 56 (quoting Crow & Manel at 430); *see also* SM Dec. at 64 ("Rodero & Crow[] describe[es] 'the grouping of Mendelian disorders associated with an up-regulation of type I interferon signaling as a novel set of human inborn errors of immunity.'").

cause . . . ."). The Special Master did not need to diagnose—and the parties agree—because the injury itself was not disputed but rather "whether the . . . vaccine [caused the injury]." *See Andreu*, 569 F.3d at 1378; Tr. at 25:8–16 ("THE COURT: Did the Special Master have to determine a diagnosis? [THE GOVERNMENT]: No. . . . [PETITIONERS]: [W]e would agree that . . . petitioner[s] can establish the burden . . . and causation without a diagnosis."). The issue of whether the H.H. suffered a vaccine-aggravated injury is properly addressed by *Loving* prongs four, five, and six. *See W.C. v. Sec'y of Health & Hum. Servs.*, 704 F.3d 1352, 1357 (Fed. Cir. 2013) (holding *Loving* to be the "correct framework for evaluating off-table significant aggravation claims") (citing *Loving ex rel. Loving v. Sec'y of Health & Hum. Servs.*, 86 Fed. Cl. 135, 144 (2005)). Here, the Special Master did diagnosis, which is permitted under *Andreu* if the diagnosis would not arbitrarily change the causation analysis under *Loving*. *Andreu*, 569 F.3d at 1381 ("[W]hatever caused [the injury] also led to [petitioner's] . . . disorder. The pivotal issue, therefore, is whether the . . . vaccine triggered [the injury]." (internal citation omitted)). Accordingly, the Court will review to determine if the Special Master's diagnosis altered causation prior to a proper causation analysis under *Loving*. *See id.*

B. Whether H.H.'s Diagnosis Subsumes Causation

An interferonopathy is a genetic autoinflammatory disease.[6] Debora d'Angelo, et al., *Type I Interferonopathies in Children: An Overview*, 9 FRONTIERS IN PEDIATRICS 1, 1 (March 31, 2021). Type I interferonopathy is a subset of interferonopathy diseases.[7] *Id.* at 2. As of 2017, 13 different type I interferonopathies have been identified. *Id.* at 6. AGS, one of the first type I interferonopathies identified, is linked with several genetic mutations and presents in a spectrum of phenotypes and severity. *Id.* A person can have a type I interferonopathy that is not AGS or AGS-like or have a type I interferonopathy with AGS-like symptoms varying in severity. *Id.*; *see also* SM Dec. at 56 ("[A]lthough the AGS diagnostic label still has a useful clinical purpose, there are many patients who do not fit this paradigm as initially delineated. Hence, we are now tending towards the use of the generic term 'type I interferonopathy'" (quoting Crow & Manel at 429)).

Petitioners argue describing the injury as AGS or AGS-like is erroneous because it goes "against the great weight of evidence presented[.]" Mot. for Review Mem. at 15. While the Special Master explored nine factors to diagnosis H.H. with AGS or AGS-like interferonopathy, petitioners maintain there "were more signs or significant characteristics that were not seen in H.H." that contradict a finding of AGS. *See* SM Dec. at 50–60 (discussing nine factors: (1) clinical presentation; (2) elevated liver enzymes; (3) elevated interferon alpha/neopterin levels; (4) genetic mutation; (5) calcifications; (6) basal ganglia damage; (7) normalization of neopterin levels; (8) onset of AGS after 12 months of age; and (9) neurological stabilization and improvement); Tr. at 20:22–21:1. Specifically, petitioners indicate the lack of a mutation in H.H., the lack of genes in H.H.'s parents, two healthy siblings, no skin lesions, no calcifications, no basal ganglia damage, no swallowing issues, no microcephaly, healthy organs, no pleocytosis, no further regression, perfect skin, and a normal life expectancy all rebut an AGS or AGS-like

[6] Interferonopathies are a "group of inherited [(genetic)] autoinflammatory diseases[.]" Debora d'Angelo, et al., *Type I Interferonopathies in Children: An Overview*, 9 FRONTIERS IN PEDIATRICS 1, 1 (March 31, 2021).
[7] Type I interferonopathies relate to an overproduction or underproduction of type I interferons who "primarily participate[] in the innate immune system response to viral antigens[.]" d'Angelo, et al., *supra* note 10, at 2.

diagnosis. Tr. at 20:16–22:1. Petitioners assert the Special Master diagnosed H.H. with AGS when an AGS diagnosis "really seems like well beyond one in a million" and "despite no medical providers who treated H.H. diagnosing him with AGS." Mot. for Review Mem. at 15 (citing Entitlement Hr'g Tr. at 290:9–291:15) (emphasis removed); Tr. at 30:1–6 ("[PETITIONERS]: AGS is a diagnosis, is a rare genetic disorder, and that is what the Special Master . . . diagnosed him with . . . despite no medical providers who . . . treated H.H. diagnosing him with AGS.").

In this case, the Special Master determined after assessing nine factors H.H. had a "genetic type I interferonopathy that is either AGS or is AGS-like." SM Dec. at 51–60, 63. The Special Master noted "[m]utations in . . . [seven] genes account for around 95% of patients with classical AGS . . . mean[ing] . . . five percent of AGS cases are associated with an unidentified genetic mutation." *Id.* at 55 (internal citations omitted). Despite H.H. not having "a gene currently identified with AGS," the Special Master still determined H.H. has "AGS or a similar genetic disorder." *Id.* at 55, 51. As the Special Master noted, "[s]everal of H.H.'s treating physicians . . . agreed that H.H.'s clinical presentation was suggestive of or consistent with AGS[,]" but no treating physician or AGS expert has been able to definitively diagnosis H.H. with AGS. *Id.* at 52. The Special Master, however, did diagnose H.H. with an AGS disorder despite no treating physician, AGS expert, or medical expert being able to. *Id.* at 52, 60 ("Dr. [V]anderver, one of the nations' leading authorities on AGS, . . . noted that H.H. had a 'suspected heritable interferonopathy.'"); *see also* Entitlement Hr'g Tr. at 296:1–4 ("[DR. BARAÑANO]: I'm not here to say . . . he definitely has AGS. He has something like AGS that in my experience we will eventually find the genetic underpinnings of his disorder.").

Whether the diagnosis is correct or not does not change the preliminary issue—whether the vaccine significantly aggravated H.H.'s injury. As established in *Andreu*, a determination of a diagnosis is not required when it does not change the underlying causation dispute; because a diagnosis may not change the outcome, however, it could be harmless. *See supra* Section VI.A; *Andreu*, 569 F.3d 1367. Therefore, the focus of the Court's inquiry is if the Special Master foreclosed a finding of significant aggravation by diagnosing H.H. *Andreu*, 569 F.3d 1367.

Petitioner argued the diagnosis excludes a fair significant aggravation analysis because the mischaracterized diagnosis permeates throughout all prongs of the *Loving* analysis. Mot. for Review Mem. at 14 ("The [d]ecision denying entitlement in this case rests largely with the Special Master diagnosing . . . H.H. with AGS or some other unknown genetic [t]ype I [i]nterferonopathy."). Petitioners object to the Special Master diagnosing H.H. with an AGS or AGS-like disorder because it "improperly mischaracterized the meaning of 'AGS-like' to suggest . . . H.H. had a genetic [t]ype I [i]nterferonopathy as opposed to the October 2013 vaccinations causing the [t]ype I [i]nterferonopathy." *Id.* The mischaracterization assumed the genetic mutation solely caused the injury when petitioners argued the injury could be genetic with a vaccine-aggravated injury in addition to the genetic injury. *Id.* "[T]he Special Master's methodology when analyzing *Loving* Prongs 4–6" was erroneous because of that assumption. *Id.* at 1. In oral argument, petitioners explained "'AGS-like' is describing the injury" with symptoms, but "not all interferonopathies have [AGS symptoms] or have a diagnosis of AGS." Tr. at 11:21–25. Petitioners' theory is H.H. has "an unknown genetic type I interferonopathy." Tr. at 8:19–20, 10:17–19, 12:10–14 ("THE COURT: [I]f there was a genetic component,

petitioners' argument is it was not AGS? [PETITIONERS]: Correct."). The Special Master, according to petitioners, regarded the injury as a normal course of AGS merely because the symptoms were AGS-like. Mot. for Review Mem. at 14. Petitioners assert this characterization disregards the possibility of a vaccine-aggravated injury compounding a pre-existing type I interferonopathy. Tr. at 31:1–5 ("THE COURT: [I]s it that the error was associated with conflating [injury and diagnosis]? That here . . . the injury as a diagnosis got merged together, and then the cause became purely genetic? [PETITIONERS]: Yes, Your Honor.").

The government argues the diagnosis from the Special Master was not incorrect, and H.H.'s injury is 100 percent caused by H.H.'s unidentified genetic mutation. Tr. at 17:1–20 ("[THE GOVERNMENT]: Special Master Oler went through, very detailed, replying on the expert reports, relying on the medical record, and the nine factors she provided was how she was able to come to this conclusion of AGS or AGS-like disease."), 11:8-11 ("THE COURT: [T]he government's position is 100 percent genetic-caused injury? [THE GOVERNMENT]: That is correct, Your Honor."). The government asserts H.H.'s injury is consistent with the "normal course of AGS" and "all because of the genetics." Tr. at 15:10–21.

The Vaccine Act focuses on tracing causation to the vaccine. The Federal Circuit has instructed "special masters are not 'diagnosing' vaccine-related injuries[,]" but rather "[t]he sole issues for the special master are, based on the record evidence as a whole and the totality of the case, whether it has been shown by a preponderance of the evidence that a vaccine caused the child's injury[.]" *Knudsen ex rel. Knudsen v. Sec'y of Health & Hum. Servs.*, 35 F.3d 543, 549 (Fed. Cir. 1994) (citing 42 U.S.C. § 300aa-13(a)(1), (b)(1)). A petitioner can allege the vaccine caused a new injury or the vaccine significantly aggravated an existing injury. *Sharpe v. Sec'y of Health & Hum. Servs.*, 964 F.3d 1072, 1078 (Fed. Cir. 2020). "[U]ntil science provides us with better answers, it is not the place of a court to assume that a child with a genetic mutation is destined to have a severe outcome." *Id.* at 1084 n.4. Additionally, the Federal Circuit has warned against attributing all symptoms or injuries to a single cause. *Knudsen*, 35 F.3d at 550. In *Knudsen*, the Federal Circuit stated,

> [p]etitioners need not explain all *other* symptoms or injuries by reference to the . . . vaccination, and the issue in vaccine cases is not to diagnose all the injuries and symptoms of the child in order to ascertain whether the diagnosis is . . . vaccine or something else. It is entirely plausible, and contemplated by the statute, that [the vaccine] may cause an [injury] at the same time that . . . something else causes [other] symptoms or injuries.

Id. In other words, case law allows for recovery of vaccine-caused injuries, whether new or the result of exacerbating a pre-existing condition. *Id.*

By mischaracterizing H.H.'s injury as a rare AGS or AGS-like interferonopathy, the Special Master attributed all of H.H.'s injury symptoms to a genetic disease when H.H.'s existing genetic injury could have been aggravated by the vaccine. The Special Master noted "additional research has led those who study [AGS] to recognize that 'the range of phenotypes associated with mutations' of AGS genes 'is much broader than previously realized[,]' . . . [and i]t is important to consider this expanded understanding of the AGS phenotype in analyzing

H.H.'s presentation." SM Dec. at 55–56. In other words, the Special Master recognized a scientific understanding of AGS and AGS-like mutations was ongoing, and the presentation of AGS was broadening to include a spectrum of symptoms (or lack of symptoms) and severities. *Id.* Consequently, an AGS or AGS-like diagnosis "assume[s] that a child with a genetic mutation is destined to have a severe outcome" even if a portion of the severity or symptoms could be attributed to vaccine aggravation. *See Sharpe*, 964 F.3d at 1084 n.4. The broad characterization of symptoms as an AGS or AGS-like diagnosis effectively eliminated the possibility of "the October 2013 vaccinations [significantly aggravating] the [t]ype I [i]nterferonopathy" even though Pentacel may have caused H.H.'s injury at the same time H.H.'s genetic mutation caused similar symptoms or injuries because the decision does not account for H.H.'s baseline if he only had an AGS or AGS-like disorder. Mot. for Review Mem. at 14; *see Knudsen,* 35 F.3d at 550 ("[T]he issue in vaccine cases is not to diagnose all the injuries and symptoms of the child in order to ascertain whether that diagnosis is . . . vaccine or something else."); *see also Sharpe*, 964 F.3d at 1087 ("Congress envisioned that children with pre-existing conditions, such as gene mutations, could potentially recover."). Accordingly, the Court will assess *Loving* prongs four, five, and six to determine if the diagnosis led to an arbitrary and capricious finding on vaccine aggravation. *See Knudsen*, 35 F.3d at 550.

VII. The Special Master's Analysis for Significant Aggravation under *Loving*

To establish causation, a petitioner can "allege that the vaccine caused the onset of [the] injuries (an onset claim) or that the vaccine significantly aggravated [a] pre-existing condition (a significant aggravation claim)." *Sharpe v. Sec'y of Health & Hum. Servs.*, 964 F.3d 1072, 1078 (Fed. Cir. 2020). For an onset claim, a petitioner must satisfy by preponderant evidence the three-prong *Althen* analysis. *Althen v. Sec'y of Health & Hum. Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005). For a significant aggravation claim, a petitioner must satisfy by preponderant evidence the *Loving* six-part test. *Loving ex rel. Loving v. Sec'y of Health & Hum. Servs.*, 86 Fed. Cl. 135, 144 (2009). The last three prongs of *Loving* are derived from *Althen* and make up the "causation in fact" analysis. *W.C. v. Sec'y of Health & Hum. Servs.*, 704 F.3d 1352, 1357 (Fed. Cir. 2013) ("The *Loving* test combines the first three *Whitecotton* factors, which establish significant aggravation, with the *Althen* factors, which establish causation."). The *Althen*/*Loving* frameworks are the established vehicles in which to analyze causation in fact. *See id.* (holding *Loving* provides the correct framework for analyzing off-table significant aggravation claims); *see also Althen*, 418 F.3d at 1278. In this case, the Special Master found a "physical sign of . . . type I interferonopathy" prior to H.H.'s Pentacel vaccination. SM Dec. at 72; *see supra* Section V.B. Under *Locane*, the Special Master's finding eliminated an onset claim and left only a significant aggravation claim. *Locane v. Sec'y of Health & Hum. Servs.*, 685 F.3d 1375, 1381 (Fed. Cir. 2012) (If "the illness was present before the vaccine was administered, logically, the vaccine could not have caused the illness."); *see supra* Section V.B.

The Special Master analyzed the first three prongs of *Loving* and found "H.H.'s deterioration is consistent with the Vaccine Act's definition of significant aggravation[.]" SM Dec. at 63. Petitioners objected only to the last three prongs of the Special Master's *Loving* analysis—the three prongs of *Althen*. Mot. for Review Mem. at 11 ("The [d]ecision . . . improperly concluded the [p]etitioners did not meet the burden of proof to establish *Loving* [p]rongs 4, 5, & 6 . . . .").

When the Special Master's diagnosis inadvertently foreclosed a significant aggravation claim, the causation analysis may have become arbitrary. *See supra* Section VI.B. The government asserts if the diagnosis was incorrect, it was harmless error because "the [S]pecial [M]aster found that petitioners failed to meet their burden under any of the three *Althen* prongs, and a failure to meet their burden under even one is dispositive and fatal to their case." Resp't's Resp. at 14. If the diagnosis subsumes causation, the Special Master may not have performed a proper causation analysis under *Loving*. *See Knudsen ex rel. Knudsen v. Sec'y of Health & Hum. Servs.*, 35 F.3d 543, 550 (Fed. Cir. 1994) ("[T]he issue in vaccine cases is not to diagnose all the injuries and symptoms of the child in order to ascertain whether that diagnosis is . . . vaccine or something else."); *see also supra* Section VI.B. Accordingly, the Court must determine whether the diagnosis caused the Special Master's analysis of *Loving* prongs four, five, and six to be arbitrary and capricious.

A. Petitioners' Medical Theory Under *Loving* Prong Four

"Under *Loving* prong [four], a petitioner need only provide 'a medical theory causally connecting [petitioner's] significantly worsened condition to the vaccination.'" *Sharpe*, 964 F.3d at 1083 (quoting *Loving*, 86 Fed. Cl. at 144). "While it does not require medical or scientific certainty, [the explanation] must still be 'sound and reliable.'" *Boatmon v. Sec'y of Health & Hum. Servs.*, 941 F.3d 1351, 1359 (Fed. Cir. 2019) (quoting *Knudsen*, 35 F.3d at 548–49). Where medical literature or epidemiological evidence is introduced, it must not be viewed "through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard[.]" *Andreu ex rel. Andreu v. Sec'y of Health & Hum. Servs.*, 569 F.3d 1367, 1380 (Fed. Cir. 2009).

The Special Master found "[p]etitioners have not presented . . . a reputable explanation in this case; as such, they have failed to present preponderant evidence in support of *Loving* prong four . . . " SM Dec. at 68. Petitioners' second objection alleges the Special Master "fail[ed] to recognize [p]etitioners' experts' medically sound theory of causation of injury[.]" Mot. for Review Mem. at 1. Petitioners assert Dr. Steinman "produced med[ical] literature that supports his theory that [vaccinations] can cause the production of interferon," and "experts agree that overproduction or an excessive amount of interferons can cause the type of injury seen in [H.H.]." *Id.* at 16. The government asserts petitioners "provided a wholly speculative theory that was not supported by the scientific literature[,]" and even if petitioners "had provided sufficient evidence to establish that Dr. Steinman's theory was possible, that would not have been sufficient to meet their burden." Resp't's Resp. at 10.

A special master's decision is often "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Hum. Servs*., 618 F.3d 1339, 1347 (Fed. Cir. 2010). "[I]t is not . . . the role of this court to reweigh the factual evidence, or to assess whether the special master correctly evaluated the evidence." *Munn v. Sec'y of Health & Hum. Servs.*, 970 F.2d 863, 871 (Fed. Cir. 1992). "If the special master has considered the relevant evidence of record, drawn plausible inferences and articulated a rational basis for the decision, reversible error will be extremely difficult to demonstrate." *Hines ex rel. Sevier v. Sec'y of Health & Hum. Servs.*, 940 F.2d 1518, 1528 (Fed. Cir. 1991). A

special master, however, cannot "cloak the application of an erroneous legal standard in the guise of a credibility determination, and thereby shield it from appellate review." *Andreu*, 569 F.3d at 1379.

Petitioners here had two occasions to provide a reputable medical theory. *See* SM Dec. at 71 n.28. First, petitioners postulated a now abandoned molecular mimicry theory.[8] *Id.* After the hearing, and at the suggestion of the Special Master, petitioners retained Dr. Lawrence Steinman, an expert neurologist. Pet'rs' Status Rep. of 14 April 2020 at 1. Dr. Steinman submitted an 18-page report and 4-page reply report "focuse[d] on 'how the components of the [Pentacel] vaccine can drive an interferon response.'" SM Dec. at 39 (quoting Steinman Rep. at 9). Dr. Steinman posited the pertussis toxin and alum found within Pentacel can cause an increase of interferons directly or through the activation of inflammasomes. Steinman Rep. at 12–13. Where a patient has a resistance to type I interferons, the activation of inflammasomes causes overproduction of type I interferons and worsens neuroinflammation. *Id.* at 14. Additionally, any imbalance of type I and type II interferons can exacerbate a type I interferonopathy. *Id.* Dr. McGeady, the government's expert who previously submitted a report and testified at the entitlement hearing, submitted a 3-page rebuttal report. Second McGeady Rep.

The first study petitioners' expert Dr. Steinman referenced is a 2014 paper about immune responses to pertussis antigens in infants and toddlers after DTaP vaccination, first authored by lead researcher Fadugba. Steinman Rep. at 12 (citing Olajumoke Fadugba et al., *Immune Responses to Pertussis Antigens in Infants and Toddlers after Immunization with Multicomponent Acellular Pertussis Vaccine*, 21 CLINICAL AND VACCINE IMMUNOLOGY 12, 1613 (2014), ECF No. 101-12 [hereinafter *Fadugba*]). Fadugba is not a study of AGS or a study where the subjects have a pre-existing interferonopathy. Fadugba at 1613–16. Dr. Steinman reviewed this research to conclude "[p]ertussis toxin induces immune responses to both gamma-interferon and to type I interferon." Steinman Rep. at 12. The government's expert, Dr. McGeady, did not address the Fabugba research directly in his rebuttal report, and the government agreed at oral argument Dr. McGeady did not reference it at all. Second McGeady Rep.; Tr. at 40:3–8. Dr. McGeady, however, "do[es] not question the assertion that component of Pentacel (and of all vaccines) activate the innate immune system . . . [and the] sequence would be expected to generate a physiologic amount of type I interferon[s.]" Second McGeady Rep. at 2–3. The Special Master's decision did not dispute the Fadugba conclusions, agreed with the study generally, and noted it "stand[s] for the proposition that DTaP vaccination results in an increase in gamma interferon[.]" SM Dec. at 65. As the study's results relate to H.H., the Special Master attempted to distinguish the Fadugba study based on the timing of study measurements and noted "these [study] levels were not measured until one month after the booster vaccination." *Id.* The Special Master did not explain how the timing of the study was consequential, and exactitude in study-to-petitioner injury timing is not part of the medical theory requirement under *Loving* prong four. *See Sharpe*, 964 F.3d at 1083 ("Under *Loving* prong [four], a petitioner need only provide a medical theory causally connecting [petitioner's] significantly worsened condition to the vaccination." (internal quotations omitted)); SM Dec. at 65. At oral argument, when pressed on the importance of the Fadugba research as it relates to

[8] At the conclusion of the entitlement hearing, the Special Master "informed [p]etitioners' counsel that the record, as it currently stood, did not enable [p]etitioners to meet their burden" and "suggested . . . retaining an additional expert neurologist[.]" SM Dec. at 4 n.7.

Loving prong four, the government also agreed Fadugba "show[s] there is an increase" as Dr. Steinman concludes. Tr. at 39:10–23 ("THE COURT: Does the government agree with the Special Master's finding that Fadugba supports Dr. Steinman's theory? [THE GOVERNMENT]: . . . [Y]es, it does show that there is an increase[.]"). Petitioners must prove their medical theory "by a preponderance of the evidence[,]" and petitioners offered Fadugba to support their medical theory. *Loving*, 86 Fed. Cl. at 143–44. While not conclusive by itself, the Special Master's—and the government's—agreement Fadugba supports the "proposition that DTaP vaccination results in an increase of gamma interferon" carries significant weight in favor of petitioners satisfying their burden to prove "a medical theory causally connecting the vaccination and the [significant aggravation]" is "more probable than not." SM Dec. at 65; *Loving*, 86 Fed. Cl. at 144 (quoting *Althen*, 418 F.3d at 1278).

The second study referenced by Dr. Steinman in support of his medical theory is a 2018 study summarizing research about the modulating effect of vaccine antigens on the body's innate immune response conducted by lead researcher and author Kooijman. Steinman Rep. at 12 (citing Sietske Koojiman et al., *Vaccine antigens modulate the innate response of monocytes to Al(OH)$_3$*, PLoS ONE 13:e0197885 (2018), ECF No. 101-13 [hereinafter *Kooijman*]). The research was performed with human blood samples whose donors did not have AGS or an interferonopathy. Kooijman at 2–3. Dr. Steinman utilizes Kooijman to show "DTaP induces type I interferons" and stimulates an "increased gene expression of [a] type I interferon[.]" Steinman Rep. at 12 (internal quotations omitted). Dr. McGeady did not directly address Kooijman or its proposition but indicated he agreed Pentacel "activate[s] the innate immune system" which in turn "generate[s] a physiologic amount of type I interferon[.]" Second McGeady Rep. at 2–3; Tr. at 43:2–5 ("THE COURT: You agree Dr. McGeady does not put forth any rebuttal evidence? [THE GOVERNMENT]: Specifically towards [Kooijman], not in his supplemental expert report."). The government agreed at oral argument the article supports an increase of interferons caused by vaccinations, but the government argued the article has not "shown that it is a plausible theory" because "it's incomplete." Tr. at 43:10–15. Under *Loving* prong four, not only is medical literature not required to prove a medical theory, but also a single piece of medical literature, like Koojiman, is not required to "identif[y] and [prove] specific biological mechanisms[.]" *Knudsen*, 35 F.3d at 549 ("[C]ausation can be found in vaccine cases . . . without detailed medical and scientific exposition on the biological mechanisms. . . . [T]o require identification and proof of specific biological mechanisms would be inconsistent with the purpose and nature of the vaccine compensation program."). The Special Master did not dispute the findings in Kooijman but quoted Kooijman, stating, "[a]fter 24 hours of stimulation, both Al(OH)3 and DTaP-stimulated monocytes showed a trend towards increased gene expression of [a] type I interferon[.]" SM Dec. at 65. Under *Loving*, petitioner must show a "medical theory causally connecting the vaccination and the [significant aggravation]" is "more probable than not." *Loving*, 86 Fed. Cl. at 144 (quoting *Althen*, 418 F.3d at 1278). The Special Master's agreement with Kooijman's proposition DTaP induces type I interferons adds further support, along with Fadugba, in favor of petitioners satisfying their burden to prove a "medical theory causally connecting the vaccination and the [significant aggravation]" is "more probable than not." *See* SM Dec. at 65 (citing Kooijman); *Loving*, 86 Fed. Cl. at 144 (quoting *Althen*, 418 F.3d at 1278).

A 2008 study summarizing the research regarding inflammasome activation by alum conducted by lead researcher and author Li is the third piece of medical literature explained and applied by Dr. Steinman. Steinman Rep. at 12 (citing Hanfen Li et al., *Cutting Edge: Inflammasome Activation by Alum and Alum's Adjuvant Effect Are Mediated by NLRP3*, 181 J. IMMUNOLOGY 17, 18 (2008), ECF No. 101-14 [hereinafter *Li*]). Li discusses a study done with mice and human macrophage cell lines without AGS or an interferonopathy given a tetanus toxoid and diphtheria toxoid vaccine comprising alum. Li at 18. Dr. Steinman discussed Li to conclude "alum in Pentacel . . . activat[es] the[] NALRP3 inflammasome, which plays a key role in inducing interferonopathies[.]" Steinman Rep. at 12. Specifically, Dr. Steinman used Li to show "[i]nflammation induced by innate immunity influences the development of T cell-mediated autoimmunity" which in turn creates an increase of interferons. *Id.* (internal quotations omitted). Dr. McGeady did not directly address whether the "alum in Pentacel . . . plays a key role in inducing interferonopathies," and at oral argument, the government was unable to answer whether Dr. McGeady specifically rebutted the Li study. *See* Steinman Rep. at 12; Tr. at 45:1–6. The government at oral argument agreed Li supports the notion "vaccines may activate . . . the inflammasome[.]" Tr. at 45:1–6. The Special Master quoted Li for the proposition "inflammasome activation by alum and alum's adjuvanticity are mediated by NLRP3 and ASC." SM Dec. at 65 (citing Li). The Special Master continued, "[i]n conclu[sion], [Li] noted that . . . NLRP3 [is] an important player in alum's adjuvant effect and [Li's results] indicate an important role for the inflammasome in the development of adaptive immunity." *Id.* at 65–66 (internal quotations omitted). The Special Master's decision did not dispute Li's conclusions. *Id.* at 65. A petitioner must prove a "medical theory causally connecting the vaccination and the [significant aggravation]" by preponderant evidence. *Loving*, 86 Fed. Cl. at 144 (quoting *Althen*, 418 F.3d at 1278). Li and the Special Master's adoption of Li's conclusion identifying "NLRP3 as an important player in alum's adjuvant effect . . . and [the] role for the inflammasome in the development of adaptive immunity [(the body's immune response)]" weigh in favor of petitioners satisfying their requirement to prove by preponderant evidence "a medical theory causally connecting the vaccination and the [significant aggravation.]" SM Dec. at 65 (citing Li); *Loving*, 86 Fed. Cl. at 144 (quoting *Althen*, 418 F.3d at 1278).

The fourth and fifth papers, both co-authored and referenced by Dr. Steinman, are the 2016 Inoue paper, summarizing studies researching the molecular and cellular mechanisms of the NLRP3 inflammasome pathway performed by lead researcher and primary author Inoue, and the 2013 Axtell paper, a review article summarizing various research studies regarding type I interferons in autoimmune diseases with primary author Axtell. Steinman Rep. at 12 (citing Makato Inoue et al., *Mechanisms to develop inflammasome-independent and interferon-β-resistant EAE with neuronal damages*, 19 NAT. NEUROSCI. 12, 1599–1609 (2016), ECF No. 101-15 [hereinafter *Inoue*]; Robert Axtell et al., *Type I Interferons: Beneficial in Th1 and Detrimental in Th17 Autoimmunity*, 44 CLINICAL REV. ALLERGY IMMUNOLOGY 2, 114–20 (2013), ECF No. 101-16 [hereinafter *Axtell*]). The Inoue research was done is in the context of experimental autoimmune encephalitis ("EAE") in mice and multiple sclerosis ("MS") in human blood cells. Inoue at 2, 7. Axtell reviewed interferon type I activity in a variety of autoimmune diseases including MS. Axtell at 1. Dr. Steinman reviewed Inoue to show "there are interferon responsive neuroinflammatory conditions[.]" Steinman Rep. at 12. Dr. Steinman discussed Axtell to demonstrate "there [is a] resistance to the therapeutic effect of type I interferon in neuroinflammation, [and] in some conditions interferon can worsen the neuroinflammation[.]"

Id. In the case of H.H., whom the Special Master diagnosed with an AGS or AGS-like neuroinflammatory disorder, the immunization would have "worsened neuroinflammation in H[.]H." Steinman Reply at 3. The government was unable to "point the Court to . . . specific references" to either article in Dr. McGeady's rebuttal or evidence that Dr. McGeady addressed the studies directly at all. Tr. at 54:19–55:21 ("THE COURT: [I]s that even possible to distinguish, him addressing [Inoue or Axtell]? [THE GOVERNMENT]: I could not point the Court to . . . specific references. I would say he just addresses their overall point."). The Special Master recognized Dr. Steinman used Inoue and Axtell for the "proposition that inflammasome activation can worsen neuroinflammation" but attempted to distinguish Inoue and Axtell because they "discuss[] [EAE] and [MS.]" SM Dec. at 66. Dr. McGeady, however, does not discount the study based on the EAE or MS distinction. Tr. 49:8–16 (the government stating Dr. McGeady had "no specific mention" of Inoue). Petitioners are merely required to "provide a medical theory causally connecting [petitioner's] significantly worsened condition to the vaccination." *Sharpe*, 964 F.3d at 1083 (internal quotations omitted). Petitioners provided Inoue and Axell in support of their medical theory, and the Special Master agreed Inoue and Axtell show "inflammasome activation can worsen neuroinflammation[,]" albeit in EAE and MS, which adds additional support to petitioners' requirement to show "a medical theory causally connecting [H.H.'s] significantly worsened condition to the vaccination" through preponderant evidence. *See id.*; SM Dec. at 66.

The sixth piece of medical literature co-authored and utilized by Dr. Steinman was the 2013 Naves study summarizing research on the roles of type I and type II interferons in modulating autoimmune neuroinflammation. Steinman Rep. at 14 (citing Rodrigo Naves et al., *The Interdependent, Overlapping, and Differential Roles of Type I and II IFNs in the Pathogenesis of Experimental Autoimmune Encephalomyelitis*, 191 J IMMUNOL., 2967–77 (2013), ECF No. 101-17 [hereinafter *Naves*]). Dr. Steinman reviewed Naves to "emphasize[] the intricate interplay of type [I] and type [II] interferons on neuroinflammation[.]" *Id.* In H.H.'s case, he "has a continued propensity to overproduce type [I] interferon[s]," so additional imbalance of interferons can exacerbate or lead to enhanced severity. *Id.* Dr. McGeady does not address Naves directly. *See* Second McGeady Rep. The Special Master stated Naves "support[s] the principle that imbalance in interferon signaling aggravates disease in EAE" but found because EAE is the animal model for MS and not interferonopathy, "[i]t is difficult to see how this point is persuasive[.]" SM Dec. at 67. Under *Loving*, petitioners were required to present evidence of a "medical theory causally connecting the vaccination and the [significant aggravation.]" *Loving*, 86 Fed. Cl. at 144 (quoting *Althen*, 418 F.3d at 1278). Petitioners provided Naves to support a "medical theory causally connecting the vaccination and the [significant aggravation]" and the Special Master agreed Naves "support[s] the principle that imbalance in interferon signaling aggravates disease in EAE[,]" another type of neuroinflammatory disease like H.H.'s neuroinflammatory interferonopathy. *See Loving*, 86 Fed. Cl. at 144 (quoting *Althen*, 418 F.3d at 1278); SM Dec. at 67. While the Special Master found the study did not apply, petitioners' use of Naves in combination with other medical literature further supports a reliable medical theory and petitioners satisfying their "more probable than not" burden. *See Loving*, 86 Fed. Cl. at 144.

The seventh piece of medical literature referenced by Dr. Steinman was the 2016 Rodero & Crow review article surveying previously published research on type I interferonopathies.

Steinman Rep. at 14 (citing Mathieu Rodero & Yanick Crow, *Type I interferon-mediated monogenic autoinflammation: The type I interferonopathies, a conceptual overview*, 213 J. EXPERIMENTAL MED. 12, 2527–38 (2016), ECF No. 101-18 [hereinafter *Rodero & Crow*]). Dr. Steinman reviewed Rodero & Crow for the "general principle that an antecedent infection or even a vaccination could be the 'stressor' that triggered the interferonopathy[.]" *Id.* In his expert reply, Dr. Steinman acknowledged "H.H. does not have an ADAR-1 mutation, but the general principle [of the study] . . . provides a foundation for impugning the immunizations in October 2013." Steinman Reply at 2. At oral argument, the government asserted Rodero & Crow was not persuasive because it related to the ADAR subset of AGS. Tr. at 64:11–22 (the government stating Rodero & Crow was not persuasive "[b]ecause H.H. doesn't have . . . ADAR, so it wouldn't be applicable."). Dr. McGeady, however, does not make this point in his rebuttal. *See* Second McGeady Rep. In fact, Dr. McGeady does not reference the Rodero & Crow article at all.[9] *Id.* The Special Master concluded Rodero & Crow "suggests that vaccination as a potential trigger for a type I interferonopathy involving an ADAR-1 mutation could be an area of study at some point in the future" but "does not provide persuasive evidence . . . in this case." SM Dec. at 67.

The Special Master discredited Naves, Inoue, Axtell, and Rodero & Crow because the research did not directly study interferonopathies or AGS. *Id.* at 67–68 (finding Naves, Inoue, Axtell, and Rodero & Crow unpersuasive because the studies were not directly analogous). The Federal Circuit has held "'[i]n a field bereft of complete and direct proof of how vaccine affect the human body,' a paucity of medical literature supporting a particular theory of causation cannot serve as a bar to recovery." *Andreu*, 569 F.3d at 1379 (citing *Daubert v. Merrell Dow Pharms., Inc*., 509 U.S. 579, 593 (1993) ("[I]n some instances well-grounded but innovative theories will not have been published . . . . Some propositions, moreover, are too particular, too new, or of too limited interest to be published.")). Medical literature is not required to prove a "medical theory causally connecting the vaccination and the [significant aggravation,]" so "to require identification and [to prove a] specific biological mechanism[] would be inconsistent with the purpose and nature of the vaccine compensation program." *Loving*, 86 Fed. Cl. at 144 (quoting *Althen*, 418 F.3d at 1278); *Knudsen*, 35 F.3d at 549. The Special Master acknowledged "there appears to be no published medical literature (to include case reports) indicating the flu, pneumonia, or Pentacel vaccines can cause or exacerbate a type I interferonopathy." SM Dec. at 67. "Dr. McGeady testified that there is also no literature suggesting the live viruses associated with these vaccines could cause one of these conditions." *Id.* (internal citation omitted). Additionally, during oral argument, the parties were not aware of any other vaccine cases with a Pentacel or pertussis injury with similar symptoms. Tr. at 62:20–25 ("THE COURT: Are you aware of any other vaccine cases with a Pentacel or pertussis injury with similar symptoms? [PETITIONERS]: No, Your Honor. . . . [THE GOVERNMENT]: I am not."). The Court makes no finding on the assessment of the medical studies, and given the rare nature of AGS and H.H.'s condition, the Court notes research on the effect of vaccines on interferonopathies or AGS may be non-existent, and therefore analogous research may be properly persuasive in this

[9] At oral argument, the government asserted Dr. McGeady referenced the Rodero & Crow article on page two of his expert report. Tr. at 69:8–9. The "Crow" references, however, refer to two other articles authored by Crow published in 2015 and 2018. *See* Crow & Manel at 429; Yanick Crow et al., *A Brief Historical Perspective on the Pathological Consequences of Excessive Type 1 Interferon Exposure In vivo*, 38 J. CLIN. IMMUNOL. 694 (2018), ECF No. 71-8.

case. *See Andreu*, 569 F.3d at 1379 ("[I]n a field bereft of complete and direct proof of how vaccine affect the human body, a paucity of medical literature supporting a particular theory of causation cannot serve as a bar to recovery." (quoting *Althen*, 418 F.3d at 1280) (internal quotations omitted)). The Court leaves the question to the Special Master on remand. *See id.*; *Knudsen*, 35 F.3d at 551 (remanding for the Special Master to reassess evidence).

After reviewing Dr. Steinman's theory, the Special Master credited Dr. McGeady and found petitioners did not meet their burden of proof. SM Dec. at 66–68. Dr. McGeady in his rebuttal report, however, did not directly address any of the medical literature put forth by Dr. Steinman. *See* Second McGeady Rep. Dr. McGeady—and the Special Master relying on Dr. McGeady—found Dr. Steinman's theory unpersuasive for two reasons: (1) "[p]etitioners' theory does not explain how vaccination caused H.H.'s innate immune response to be so 'massively exaggerated as demonstrated by the elevated levels of interferon alpha in the blood and cerebrospinal fluid"; and (2) "Dr. Steinman did not explain how H.H.'s interferon alpha levels remained elevated for years after vaccination." SM Dec. at 66. The Special Master stated the literature cited by Dr. Steinman "does not suggest that [the increased interferon levels] are excessive. . . . Neither [Fadugba nor Kooijman] suggests that interferon production post-DTaP vaccination is anything resembling H.H.'s interferon alpha levels[.]" *Id.* Further, the Special Master found the theory does not explain H.H.'s persistently elevated levels. *Id.* at 67 ("Petitioners' theory is equally unpersuasive in preponderantly establishing that vaccination can cause persistently elevated levels of interferon alpha.").

The Federal Circuit summarized in *Sharpe*, a case alleging significant aggravation of petitioner's pre-existing encephalopathy, "[p]etitioner [is] required to present a medically plausible theory demonstrating that a vaccine 'can' cause a significant worsening of [the disorder]." *Sharpe*, 964 F.3d at 1083. In other words, a petitioner at *Loving* prong four is not required to show injury did happen—"did cause" is the subject of prong five—but petitioners must explain how Pentacel could exacerbate H.H.'s pre-existing AGS or AGS-like disorder, resulting in greater injury than what H.H.'s baseline was with only AGS. *See id.*; *Loving*, 86 Fed. Cl. at 144. The Special Master found "[w]hile vaccines may activate the inflammasome, Dr. Steinman has not presented a link between such activation and the development of AGS or a similar type I interferonopathy." SM Dec. at 66. Petitioners disagreed and pointed specifically to the Inoue and Axtell studies as support for the link between activation and the development of AGS. Tr. at 45:23–46:14 ("[PETITIONERS]: The link is that Pentacel can trigger type I and type II interferon response by triggering the NLRP3 inflammasomes . . . [which] causes an overproduction of interferon, and that can be explained. . . . [by] a resistance in some forms of neuroinflammation to the normal beneficial response of interferons. . . . [U]nchecked interferon production drives neuroinflammation, which then can cause severe central nervous system damage."), 46:19–24 (petitioners agreeing Dr. Steinman showed a link between inflammasome activation and a development of AGS or similar type I interferonopathy). The question here is not whether there was "activation and . . . development of AGS or a similar type I interferonopathy" as the Special Master suggested but rather if the Pentacel vaccine could have caused additional injury on top of H.H.'s pre-existing type I interferonopathy. *See Sharpe*, 964 F.3d at 1083; SM Dec. at 66. The Special Master also rejects Dr. Steinman's medical theory because of what actually happened—persistent, elevated levels—in H.H.'s case; this reasoning

confuses the prong-four requirement with the prong-five requirement. *See Sharpe*, 964 F.3d at 1083.

Petitioners' expert, Dr. Steinman, did provide a theory supported by medical research explaining the Pentacel vaccine can cause an increase in interferons as a normal innate immune response and through activation of inflammasomes, which "would be additive to what is already . . . ongoing in [H.H.]." Steinman Reply at 2. For H.H., "an underlying AGS condition"—a neuroinflammation disease which by its nature already increases interferon production—would have worsened with the administration of the vaccination. *Id.* at 3. Dr. Steinman utilized Fadugba and Kooijman as support in explaining the pertussis toxin in the Pentacel vaccine could cause an increase in interferons. Steinman Rep. at 12. The Special Master attempted to distinguish Fadugba due to the timing of measurements but did not explain how timing was consequential or why an exactitude in study-to-petitioner injury timing is required under *Loving*. *See Sharpe*, 964 F.3d at 1083 ("Under *Loving* prong [four], petitioners need only provide a medical theory causally connecting petitioner's significantly worsened condition to the vaccination." (internal quotations omitted)); SM Dec. at 65. Accordingly, the Special Master's finding on timing was arbitrary and capricious and therefore error. Dr. Steinman reviewed Li to show alum, a component of Pentacel, can trigger a type I or type II interferon response or increase by triggering the NLRP3 inflammasomes and the activation of inflammasomes. Steinman Rep. at 12. Dr. Steinman reviewed Inoue and Axtell to show resistance to type I interferons and inflammasome activation can worsen neuroinflammation, like an AGS or AGS-like disorder. *Id.* Dr. Steinman utilized Naves to support the notion any imbalance of type I and type II interferons can exacerbate a type I interferonopathy, a pre-existing condition H.H. was purported to have. *Id.* at 14. Lastly, Dr. Steinman reviewed Rodero & Crow to support the proposition of a vaccination triggering an interferonopathy. *Id.* While one piece of medical literature by itself does not necessarily establish a reliable medical theory, the principles supported by the research studies discussed by Dr. Steinman—and the Special Master's general agreement with the research studies' propositions—cumulatively carry significant weight in favor of petitioners satisfying their burden to prove "a medical theory causally connecting the vaccination and the [significant aggravation]" that is "more probable than not." *See Sharpe*, 964 F.3d at 1083 ("Under *Loving* prong [four], a petitioner *need only provide* a "medical theory causally connecting [petitioner's] significantly worsened condition to the vaccination.'" (emphasis added)).

The arbitrary and capricious standard "is a highly deferential standard of review[:] [i]f the special master has considered the relevant evidence of record, drawn plausible inferences and articulated a rational basis for the decision, reversible error will be extremely difficult to demonstrate." *Hines*, 940 F.2d at 1528. Here, the Special Master agreed "the literature cited by Dr. Steinman does demonstrate that vaccination causes the production of some amount of interferon" yet did not find petitioners met their burden to prove their "medical theory causally connecting the vaccination and the [significant aggravation]" is "more probable than not." SM Dec. at 66, 68; *see Sharpe*, 964 F.3d at 1083. Dr. Steinman opined "if there was an underlying AGS condition in play in H[.]H[.], . . . the immunization would have worsened neuroinflammation in H[.]H." Steinman Reply at 3. As discussed *supra*, Dr. Steinman's medical theory cited seven related research studies supporting his expert conclusions. Steinman Rep. at 12–14. While the Special Master concluded petitioners did not prove a medical theory

for significant aggravation, the analysis did not address H.H.'s pre-existing condition or what H.H.'s normal AGS baseline would be when the Special Master generally discredited Dr. Steinman's theory as not suggesting "anything resembling H.H.'s interferon alpha levels" or the "persistently elevated levels of interferon alpha"—when some degree of persistent elevated interferon level is a characteristic of a baseline AGS or AGS-like disorder. SM Dec. at 66–67. Disregarding H.H.'s pre-existing condition when analyzing whether Pentacel could worsen H.H.'s condition and discarding Dr. Steinman's theory positing Pentacel "would have worsened neuroinflammation" is error. [10] *Sharpe*, 964 F.3d at 1086 ("A significant aggravation claim, by definition, requires a petitioner to have a pre-existing injury." (quoting *Loving*, 86 Fed. Cl. at 144)), 1080 ("[A] petitioner must establish . . . 'a medical theory causally connecting such a significantly worsened condition to the vaccination[.]'") (quoting *Loving*, 86 Fed. Cl. at 144)); Steinman Reply at 3 ("[T]he immunization would have worsened neuroinflammation in H[.]H."); SM Dec. at 53–55, 57–58, 66–67 (concluding petitioners "failed to present preponderant evidence in support of *Loving* prong four" because petitioners could not explain persistent elevated levels—a symptom present in AGS). This consideration is especially pronounced because the government agreed their expert Dr. McGeady did not address any of the research Dr. Steinman's opinion extensively reviewed supporting his medical theory. Tr. at 40:3–8 ("THE COURT: Did your expert, Dr. McGeady, cite to any medical studies that rebut Fadugba? [THE GOVERNMENT]: Not for the proposition that there is an increase[.]"), 43:2–5 ("THE COURT: You agree Dr. McGeady does not put forth any rebuttal evidence [to Kooijman]? [THE GOVERNMENT]: Specifically towards [Kooijman], not in his supplemental expert report."), 54:19–55:21 ("THE COURT: [I]s that even possible to distinguish, him addressing [Inoue or Axtell]? [THE GOVERNMENT]: I could not point the Court to . . . specific references. I would say he just addresses their overall point."), 55:18–21 ("[THE COURT]: Do you agree that Dr. McGeady does not address [Axtell] directly? [THE GOVERNMENT]: I agree he does not address Axtell directly."); *see* Tr. at 45:1–6 (the government unable to answer where Li is rebutted). The Court finds the Special Master's conclusion regarding *Loving* prong four is accordingly unsupported in discussion with the medical literature, was not evaluated in light of a significant aggravation claim, and is therefore arbitrary and capricious. *See Saunders v. Sec'y of Health & Hum. Servs.*, 25 F.3d 1031, 1033 (Fed. Cir. 1994) ("Fact findings are reviewed . . . under the arbitrary and capricious standard; legal questions under the 'not in accordance with law' standard; and discretionary rulings under the abuse of discretion standard."); *see also Paluck v. Sec'y of Health & Hum. Servs.*, 786 F.3d 1373, 1380 (Fed. Cir. 2015) ("Where, as here, a special master . . . makes factual inferences wholly unsupported by the record, the Court of Federal Claims is not only authorized, but

[10] The Special Master's decision either does not contemplate H.H.'s pre-existing condition and already elevated interferons or attributes the full severity of his injury to an unidentified genetic mutation, foreclosing a significant aggravation claim. SM Dec. at 55 ("[T]here was no explanation for H.H.'s elevated neopterin and interferon alpha levels other than AGS."), 56 (adopting an "expanded understanding of the AGS phenotype" to include all of H.H.'s current symptoms as part of his AGS or AGS-like disorder), 58 (crediting the opinions of Drs. McGeady and Barañano stating there is "variability in AGS presentation" and "normal development before the onset of symptoms in AGS . . . should not be considered as a finding implicating the vaccines"), 60 (attributing "H.H.'s rapid and relentless decline" to the start of the disease process rather than a potential vaccine aggravation), 66 (discrediting Dr. Steinman's theory because it did explain excessive interferon levels, a symptom characteristic of AGS, when H.H.'s interferon alpha levels were "the highest neopterin levels [one provider had] ever seen"), 67 (discrediting Dr. Steinman's theory because it did not address "persistently elevated levels[,]" a symptom characteristic of AGS and a component of H.H.'s condition).

obliged, to set aside the [S]pecial [M]aster's findings of fact and conclusions of law."). The Court leaves the ultimate conclusion to the Special Master on remand regarding whether H.H.'s pre-existing condition can be aggravated as explained by Dr. Steinman's medical theory on "how the components of the [Pentacel] vaccine can drive an interferon response" leading to "worsening neuroinflammation in H[.]H." and whether this theory satisfies the *Loving* standard. Steinman Rep. at 9; Steinman Reply at 3; *see Sharpe*, 964 F.3d at 1083.

B. Logical Sequence of Cause and Effect under *Loving* Prong Five

Under *Loving* prong five, a petitioner must show by preponderant evidence "a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation." *Loving*, 86 Fed. Cl. at 144. For satisfying the fifth *Loving* prong, "medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether 'a logical sequence of cause and effect show[s] that the vaccination was the reason for the injury.'" *Capizzano v. Sec'y of Health & Hum. Servs*., 440 F.3d 1317, 1326 (Fed. Cir. 2006) (quoting *Althen*, 418 F.3d at 1280).

The Special Master found "[p]etitioners have not presented evidence demonstrating that H.H. experienced a vaccine-associated significant aggravation of his interferonopathy, signs of which had already begun to manifest by the time he received his Pentacel vaccine. They do not point to any testing or clinical signs that suggest vaccine causation." SM Dec. at 68. The Special Master continued, "[petitioners] do not point to any testing or clinical signs that suggest vaccine causation. Instead, they assert that because H.H.'s deterioration occurred close-in-time to his vaccinations, and because no alternate explanation exists, then the vaccines 'did cause' a significant aggravation of H.H.'s condition." *Id.* The Special Master also found the elevated transaminase levels and lack of a severe local reaction are not supported by petitioners' causation theory. *Id.* ("[T]he records contain evidence supporting the opposite position—that the vaccines did not affect his condition.").

The Special Master further discredited "several of H.H.'s treating doctors [who] opined that the vaccines he received caused his condition." *Id.* at 69. For instance, the Special Master discredited Dr. Hollis, H.H.'s treating physician, who concluded H.H.'s "rapid decline can be attributed to receiving the vaccinations on October 17, 2013 and October 23, 2013," because "[s]he did not articulate a theory of causation." *Id.* Additionally, the Special Master discredited Dr. Marks, H.H.'s treating neurologist, who opined the vaccines H.H. received caused his condition, because his theory of causation—a theory of molecular mimicry which was abandoned and replaced by Dr. Steinman's theory—was unpersuasive. *Id.* 69–71 ("Dr. Marks' inability to persuasively articulate a theory of causation caused me to afford his opinion less weight.").

Petitioners allege in their third objection the Special Master "devalued the expert opinion of petitioners' [sic] expert" who "provided evidence sufficient to satisfy [p]rongs 5 and 6 of *Loving* when discussing whether the Pentacel vaccination significantly aggravated H.H.'s injury, which would also satisfy *Althen*." Mot. for Review Mem. at 18. Petitioners argue the Special Master's suggestion all symptoms in H.H.'s medical record should be explained by the causation theory is incorrect. Tr. 80:2–21. Petitioners explained they are "not seeking to prove what

raised his transaminases . . . . [They] have put forth a . . . medical theory that the vaccination caused an AGS-like interferonopathy and damage." *Id.* at 80:13–21. The government argues the mere showing of a proximate temporal relationship between the vaccine and injury is insufficient to satisfy *Loving* prong five. Resp't's Resp. at 11 (citing *Moberly*, 592 F.3d at 1323). The government further argues there are symptoms Dr. Steinman's theory does not explain. Tr. at 81:7–12 ("[THE GOVERNMENT]: [T]hey haven't shown that there was a vaccine reaction after the Pentacel to fit in Dr. Steinman's theory. [T]he liver enzymes . . . there's nothing about petitioners' theory that would explain that.").

The Special Master's underlying assumption—"H.H.'s presentation" can be attributed to an "expanded understanding of the AGS phenotype"—devalued evidence supporting significant aggravation. SM Dec. at 56; *see supra* Section VI.B. The Special Master found "petitioners have not presented evidence demonstrating that H.H. experienced a vaccine-associated significant aggravation of his interferonopathy, signs of which had already begun to manifest by the time he received his Pentacel vaccine." SM Dec. at 68. In *Sharpe*, a case with a pre-existing condition caused by a genetic mutation, there was a similar assumption, and the special master found petitioner failed to meet *Loving* prong five "because, in part, 'it is quite likely that [the injury] in fact began prior to vaccination.'" *Sharpe*, 964 F.3d at 1086. The Federal Circuit rejected this reasoning stating, "[a] significant aggravation claim, by definition, requires a petitioner to have a pre-existing injury. . . . Thus, that [petitioner] experienced some [injury] before receiving her vaccination should have no negative effect on [p]etitioner's case." *Id.* The government's experts, Drs. McGeady and Barañano, whom the Special Master credits, both opined "there is variability in AGS presentation" including variety of symptoms (or lack thereof) and severity, but the Special Master's decision does not contemplate a mild case of AGS with the vaccine worsening the disorder because the Special Master attributes all injury to the underlying genetic mutation. SM Dec. 58 ("Both Dr. McGeady and Dr. Barañano opined that there is variability in AGS presentation . . . ."), 68 (finding no signs of significant aggravation because signs "had already begun to manifest by the time [H.H.] received his Pentacel vaccine"). Characterizing H.H.'s injury as AGS or AGS-like and attributing all symptoms of an "expanded understanding of the AGS phenotype" to a "severe outcome" because of his genetic mutation caused the Special Master's finding on *Loving* prong five to be arbitrary and capricious because it ignored vaccine aggravation. SM Dec. at 58; *see Knudsen*, 35 F.3d at 550; *Sharpe*, 964 F.3d at 1086.

In the prong-four analysis, the Special Master rejected Dr. Steinman's theory because it does not explain "massively exaggerated" response or how levels "remained elevated for years after vaccination." SM Dec. at 66. While a pre-existing condition "should have no negative effect on the petitioners' case," the pre-existing condition cannot be completely ignored as the severity and symptoms of a purely genetic disorder is instructive in determining if a vaccine aggravated the pre-existing condition. *See Knudsen*, 35 F.3d at 550; *Sharpe*, 964 F.3d at 1086. Here, "a significant aggravation claim, by definition, requires a pre-existing condition," and the Special Master ignored the fact "persistent elevation of H.H.'s neopterin levels" and "elevated levels of [interferon]-alpha" is diagnostic for AGS, the disorder the Special Master found H.H. to have. SM Dec. at 53–55, 57, 68–69; *see Sharpe*, 964 F.3d at 1086; *supra* Section VI.B. The Court finds this to be erroneous because the Special Master ignored the possibility of vaccine aggravation. *See Knudsen*, 35 F.3d at 550; *Sharpe*, 964 F.3d at 1086.

When the Special Master found the medical records failed to support a vaccine-aggravated injury, the Special Master pointed to the lack of a local reaction and elevated transaminases as evidence against a vaccine aggravated injury. SM Dec. at 69 ("Petitioners have not explained how this finding fits into their causation theory. Dr. McGeady opined that there was no medical literature supporting such a connection."). A petitioner "need not explain other symptoms" associated with the pre-existing condition but rather a petitioner must prove "the vaccination caused his significant aggravation." *Id.*; *Knudsen*, 35 F.3d at 550; *Loving*, 86 Fed. Cl. at 144. In *Knudsen*, a case reviewing whether a vaccine or a viral infection caused the petitioner's injury, the Federal Circuit held "petitioners need not explain all *other* symptoms or injuries by reference to the . . . vaccination, and the issue in vaccine cases is not to diagnose all the injuries and symptoms of the child in order to ascertain whether the diagnosis is [vaccine] or something else." *Knudsen*, 35 F.3d at 550. By requiring petitioners to explain all symptoms (or lack thereof), the Special Master ignored the crux of a significant aggravation claim—"a significant aggravation claim, by definition, requires a petitioner to have a pre-existing injury," and other symptoms could be attributed to the pre-existing condition, not the vaccine-aggravated injury. *See Sharpe*, 964 F.3d at 1086. While the Special Master required petitioners' medical theory to account for all symptoms, the Vaccine Act does not impose such a burden but only requires showing the vaccination "caused significant aggravation," and accordingly the Court finds this to be error. SM Dec. at 68–69; *see Knudsen*, 35 F.3d at 550 ("[P]etitioners need not explain all *other* symptoms or injuries by reference to the . . . vaccination, and the issue in vaccine cases is not to diagnose all the injuries and symptoms of the child in order to ascertain whether the diagnosis is [vaccine] or something else."); *Loving*, 86 Fed. Cl. at 144 (holding a petitioner must show "a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation").

Evidence for *Loving* prongs four and five often overlap. *Knudsen*, 35 F.3d at 548 ("This logical sequence of cause and effect must be supported by a sound and reliable medical or scientific theory." (internal quotations omitted)); *Moriarty v. Sec'y of Health & Hum. Servs.*, 844 F.3d 1322 (Fed. Cir. 2016) ("There is 'no reason why evidence used to satisfy one of the [*Althen*] prongs cannot overlap to satisfy another prong.'" (quoting *Capizzano*, 440 F.3d at 1326)). The Federal Circuit has suggested "in certain cases, a petitioner can prove a logical sequence of cause and effect between a vaccination and the injury . . . with a physician's opinion to that effect where the petitioner has proved that the vaccination *can cause* the injury . . . and that the vaccination and injury have a close temporal proximity[.]" *Sharpe*, 964 F.3d at 1086 n.5 (citing *Moriarty*, 844 F.3d at 1333 (emphasis added)). The Special Master dismissed the physicians' opinions concerning whether the vaccine caused H.H.'s injury because they "could not articulate a medical theory." SM Dec. at 69 ("[Dr. Hollis] did not articulate a theory of causation"), 71 ("Dr. Marks' inability to persuasively articulate a theory of causation caused me to afford his opinion less weight."). The replacement of the theory after the entitlement hearing, however, should not devalue the treating physicians' opinion of H.H.'s injury being aggravated by the vaccine because prong five does not require a treating physician to opine on a medical theory to find their testimony persuasive—only prong four requires opinion on a medical theory. *See Andreu*, 569 F.3d at 1375 ("[T]reating physicians are likely to be in the best position to determine whether a logical sequence of cause and effect show[s] that the vaccination was the reason for the injury."); *Loving*, 86 Fed. Cl. at 144 (holding a petitioner must show "a logical

sequence of cause and effect showing that the vaccination was the reason for the significant aggravation"); Pet'rs' Ex. 66 at 3, ECF No. 43–3 (Dr. Hollis Affidavit) ("It is my opinion that H.H.'s severe and rapid developmental regression is unusual for a previously healthy child. Many diagnoses have been evaluated and ruled out . . . . It seems to me that his rapid decline can be attributed to receiving the vaccinations on October 17, 2013 and October 23, 2013."); Pet'rs' Ex. 67 at 3–4, ECF No. 43–4 (Dr. Marks Affidavit) ("It is my opinion that it was quite unusual for a previously asymptomatic patient to develop such severe and rapidly progressing dystonia with encephalopathy at this age. . . . I have concluded that H.H.'s exposure to the fifteen (15) month vaccines was within a reasonable medical probability, the most likely trigger for him to develop rapidly progressing dystonia with encephalopathy to this degree."). *Loving* prong five is "supported" by *Loving* prong four, and the Court finds the Special Master's analysis of *Loving* prong four to be arbitrary and capricious. *See Knudsen*, 35 F.3d at 548 ("This logical sequence of cause and effect must be supported by a sound and reliable medical or scientific theory."); *supra* Section VII.A. As the record contains evidence of the treating physicians opining H.H.'s injuries were aggravated by the vaccinations, the Special Master's *Loving* prong five is not supported by the record, and the Court must remand the case. Dr. Hollis Affidavit at 3; Dr. Marks Affidavit at 3–4; *see Paluck*, 786 F.3d at 1380 ("Where, as here, a special master . . . makes factual inferences wholly unsupported by the record, the Court of Federal Claims is not only authorized, but obliged, to set aside the [S]pecial [M]aster's findings of fact and conclusions of law."). The Court makes no finding on whether logical sequence is proven and leaves open the question of whether *Loving* prong five is met in light of Dr. Steinman's report on significant aggravation to the Special Master on remand. *See Sharpe*, 964 F.3d at 1383; *Knudsen*, 35 F.3d at 548.

C. Proximate-Temporal Relationship under *Loving* Prong Six

Prong six of the *Loving* test requires "a showing of a proximate temporal relationship between the vaccination and the significant aggravation." *Loving*, 86 Fed. Cl. at 144. "[T]he proximate temporal relationship prong requires preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." *de Bazan v. Sec'y of Health & Hum. Servs*., 539 F.3d 1347, 1352 (Fed. Cir. 2008).

Petitioners' third objection argues Dr. Steinman's medical theory provides a three-week interval in which symptoms worsened. Mot. for Review Mem. at 18; Tr. at 88:8–17 ("[PETITIONERS]: [I]t's petitioners' contention that Dr. Steinman's report and the literature he provided sufficiently demonstrates that H.H.'s onset was within a medically reasonable time frame, and we contend that there were early signs immediately after the Pentacel vaccine . . . and that the completion of his damage was done in approximately three weeks."). The government argues Dr. Steinman's theory is not sufficiently supported. Tr. at 87:8–10 ("[THE GOVERNMENT]: Dr. Steinman [is] just saying that three weeks, without the proper support, doesn't meet petitioners' burden.").

In her two-page analysis regarding proximate-temporal relationship, the Special Master found petitioners failed to prove either "H.H.'s type I interferonopathy either began or was significantly aggravated three weeks after the Pentacel vaccin, or . . . [p]etitoners have

preponderantly established that the three weeks post vaccination is a medically acceptable onset interval." SM Dec. at 74. The Special Master noted Dr. Steinman's three-week interval is based on a direct causation claim theory because there was not "any symptomatology related to an interferonopathy" until "three weeks after the Pentacel immunization on October 23, 2013." *Id.* at 72. The Special Master concluded Dr. Steinman's "opinion regarding the appropriateness of the onset interval" was based on an onset theory, not a significant aggravation theory. *Id.* Dr. Steinman explains in his reply, however, "I have covered the two alternatives in describing either a theory based on direct causation or on significant aggravation. The onset of neuroinflammation within [three] weeks of the October 23, 2013 immunizations with Pentacel is consistent with [Schonberger] and [Bennetto & Scolding], which cover related neuroinflammatory conditions of the peripheral . . . and central nervous systems[.]" Steinman Reply at 3. Petitioners asserted Dr. Steinman's medical theory provides a three-week onset for both direct causation and significant aggravation. Tr. at 88:8–11 ("[PETITIONERS]: [I]t's petitioners' contention that Dr. Steinman's report and the literature he provided sufficiently demonstrated that H.H.'s onset was within a medically reasonable time frame, and we contend that there were very early signs immediately after the Pentacel vaccine, within days, and that the completion of his damage was done in approximately three weeks."). The Special Master does not consider Dr. Steinman's theory relating to significant aggravation because the Special Master found her "determination in this case is contrary to Dr. Steinman's" opinion regarding the onset of symptoms. SM Dec. at 72. The Special Master's characterization of Dr. Steinman's theory to only include direct causation when he opined "on significant aggravation" is arbitrary and capricious because the Special Master did not consider Dr. Steinman's theory on significant aggravation in the record. *See* Steinman Reply at 3; *Hines*, 940 F.2d at 1528 ("If the [S]pecial [M]aster has considered the relevant evidence of record, drawn plausible inferences and articulated a rational basis for the decision, reversible error will be extremely difficult to demonstrate.").

The Court finds, as discussed *supra* Section VII.A, the Special Master's *Loving* prong-four analysis was arbitrary and capricious and because "a temporal relationship is closely related to the underlying medical theory" required by prong four, the Court also reviews for error the causation analysis under *Loving* prong six. *See Capizzano*, 440 F.3d at 1326.[11] Despite the Special Master stating Dr. Steinman did not opine on significant aggravation, the Special Master did continue to analyze *Loving* prong six in light of significant aggravation. SM Dec. at 73 ("Naves . . . does not support the position that an interferonopathy would begin or become significantly aggravated either on the same day or within one or two days after a trigger."). The Special Master concluded, "I do not find H.H.'s type I interferonopathy either began or was significantly aggravated three weeks after the Pentacel vaccine[,]" but did not provide an analysis to discuss the timeline of H.H.'s injuries or whether H.H.'s injuries were significantly aggravated. *Id.* at 74. The Special Master did not "articulate a rational basis for her decision" nor is her decision supported by the record because the Court finds her analysis under *Loving*

[11] In *Pafford*, a case involving the development of Still's disease following vaccination, the Federal Circuit emphasized "evidence demonstrating petitioner's injury occurred within a medically acceptable time frame bolsters a link between the injury alleged and the vaccination at issue under the 'but-for' prong of causation analysis." *Pafford v. Sec'y of Health & Hum. Servs.*, 451 F.3d 1352, 1358 (Fed. Cir. 2006). Finding a temporal relationship is also closely related to the underlying medical theory of the injury. *Capizzano*, 440 F.3d at 1326 ("We see no reason why evidence used to satisfy one of the [*Loving*] prongs cannot overlap to satisfy another prong.").

prong four to be arbitrary and capricious. *See Hines*, 940 F.2d at 1528; *see also Paluck*, 786 F.3d at 1380 ("Where, as here, a special master misapprehends a petitioner's theory of causation, misconstrues his medical records, and makes factual inferences wholly unsupported by the record, the Court of Federal Claims is not only authorized, but obliged, to set aside the [S]pecial [M]aster's findings of fact and conclusions of law."); *Andreu*, 569 F.3d at 1375 (concluding that a special master erred in disregarding probative testimony from a petitioner's treating physicians). The Court remands and leaves the ultimate conclusion to the Special Master regarding whether there was a proximate-temporal relationship in light of Dr. Steinman's opinion stating aggravation would occur within three weeks and whether this theory satisfies *Loving* prong six. *See* Steinman Reply at 3 ("I have covered the two alternatives in describing either a theory based on direct causation or on significant aggravation"); *see also Capizzano*, 440 F.3d at 1326 ("We see no reason why evidence used to satisfy one of the [*Loving*] prongs cannot overlap to satisfy another prong.").

VIII. Conclusion

For the foregoing reasons, the Court **SUSTAINS** the Special Master's decision relating to the influenza and pneumonia vaccinations as petitioners did not meet their burden of proof under the *Loving/Althen* frameworks. The Court **VACATES** the Special Master's decision finding Pentacel did not significantly aggravate H.H.'s type I interferonopathy because the Special Master erred by assuming H.H.'s injury and diagnosis was purely genetically caused before starting the *Loving* analysis. The Court therefore **GRANTS IN PART** petitioners' motion for review and **REMANDS** to the Special Master to determine whether petitioners can satisfy *Loving* prongs four, five, and six for significant aggravation by Pentacel.

IT IS SO ORDERED.

s/ Ryan T. Holte
RYAN T. HOLTE
Judge